17823

TSCA HEALTH & SAFETY STUDY COVER SHEET

TSCA CBI STATUS:

- **CHECK IF THIS PAGE CONTAINS CONFIDENTIAL BUSINESS INFORMATION (CBI)**
  Clearly mark the confidential information with bracketing and check the box in the appropriate section (☐ *Contains CBI*).
  Submit a sanitized cover sheet with CBI deleted. Mark the sanitized copy, "Public Display Copy" in the heading.

1.0 SUBMISSION TYPE - *Contains CBI*

☐ 8(d) **XX 8(e)** ☐ FYI ☐ 4 ☐ OTHER: Specify 8EHQ-0299-14387

X Intial Submission ☐ Follow-up Submission ☐ Final Report Submission

Previous EPA Submission Number or Title if update or follow-up: Docket Number, if any: #

☐ continuation sheet attached

2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e): optional for §4, 8(d) & FYI)	**2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID**	**2.3 FOR EPA USE ONLY**
X- YES ☐ NO	P917-006-894 ~~99-2-17~~	

3.0 CHEMICAL/TEST SUBSTANCE IDENTITY - *Contains CBI*

Reported Chemical Name (specify nomenclature if other than CAS name):

CAS# : 181274-15-7

2-((((4-Methyl-3-propoxy-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl)carbonyl)-amino)-Sulfonyl)-benzoic acid-methyl-ester Na

Purity _98.1__%

X- Single Ingredient

☐ Commerical/Tech Grade

☐ Mixture *Trade Name:* MKH 6561 *Common Name:* Sulfonamide

CAS Number	*NAME*	*% WEIGHT*

Other chemical(s) present in tested mixture

☐ continuation sheet attached

99 FEB 23 AM 7:40 RECEIVED

4.0 REPORT/STUDY TITLE ☐ *Contains CBI*

Developmental Toxicity Study in Rabbits After Oral Administration, Report # 27466

8EHQ-99-14387

continuation sheet attached

5.1 STUDY/TSCATS INDEXING TERMS

[CHECK ONE]

HEALTH EFFECTS (HE): X ENVIRONMENTAL EFFECTS (EE): _____ ENVIRONMENTAL FATE (EF): _____

5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes)

STUDY TYPE: _DTOX SUBJECT ORGANISM (HE, EE only): _RABB_ ROUTE OF EXPOSURE (HE only): _____ VEHICLE OF EXPOSURE (HE only)_

Other: Other: *Other:* *Other:*

6.0 REPORT/STUDY INFORMATION ☐ *Contains CBI* X - Study is GLP

Laboratory _Bayer AG Toxicology Lab, Wuppertal, Germany Report/Study Date_4/30/98_

Source of Data/Study Sponsor (if different than submitter) _____ Number of pages _588_

☐ continuation sheet attached

7.0 SUBMITTER INFORMATION ☐ *Contains CBI*

Submitter: Donald W. Lamb Title: VP, Product Safety & Regulatory Affairs Phone: 412-777-7431

Company Name: Bayer Corporation

Company Address: 100 Bayer Road, Pittsburgh, PA. 15205 Submitter Address (if different): _____

Technical Contact: ___Same as above Phone: ( )_____

☐ continuation sheet attached

8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS - *Contains CBI*

Note: This substance is an experimental herbicide

☐ continuation sheet attached

Submitter Signature: Donald W Lamb **Date:** 2/16/99

Page__1__of__2__

99 MAR 31 AM 9:40 RECEIVED OPPT NCIC

CONTAINS NO CBI

88900010S

9.0 CONTINUATION SHEET

TSCA CBI STATUS:

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Submitter Tracking Number/Internal ID

P917 006 894
99-2-17

Continuation of 2.1

This study is being reported based on the findings of increased abortions, postimplantation loss, and retarded ossification at doses of 500 or 1000 mg/kg/day. The fact that these findings were most likely due to maternal toxicity observed at the 500 and 1000 mg/kg doses does not negate the potential requirement to report this study.

Abstract

Twenty-two female Himalayan rabbits were treated daily, by gavage, with MKH 6561 in 0.5 % carboxymethylcellulose from days 6 to 28 p.c. at doses of 0, 20, 100, 500, or 1000 mg/kg/day. On day 29 of gestation the fetuses were delive-red by cesarean section.

Doses of 500 and 1000 mg/kg resulted in symptoms (cold ears, alopecia, or swelling of vulva), abortions, decreased feed and water intake, and body weight loss. Furthermore, in the 500 and 1000 mg/kg dose groups there were compound-related effects on the gastrointestinal tract (anal prolapse, diarrhea, light colored feces, solid contents in the stomach, enlarged cecum with gaseous contents or fluid, or light discoloration of the small intestine) and on the liver (increased blood values for cholesterol, triglycerides, total bilirubin and GLDH, decreased protein levels in the blood, distinct lobulation or light discoloration of the liver, or decreased liver weight). Also, effects on the thyroid hormones (decreased T3 and T4 values, or increased thyroxine-binding capacity in the blood) were evident in the 500 and 1000 mg/kg dose groups. In the 500 mg/kg dose group, some of these effects were limited to the single female which aborted (see below), while all females were affected in the 1000 mg/kg group.

The gestation rate was marginally decreased by one abortion in the 500 mg/kg dose group and severely decreased by 18 abortions in the 1000 mg/kg dose group. These abortions were most likely due to systemic maternal toxicity rather than a specific effect on reproduction.

The placental weights were distinctly decreased, and the placentas were coarse grained and pale in the 1000 mg/kg dose group. The postimplantation loss in females with viable fetuses was slightly increased and correspondingly the number of fetuses was slightly decreased in the 1000 mg/kg dose group. There was no compound-related effect on fetal sex distribution. Fetal weight was severely decreased, and correspondingly skeletal ossification was retarded in the 1000 mg/kg dose group. Furthermore, an increased incidence of fetuses with distinct lobulation of the liver (variation) in the 1000 mg/kg dose group could not be excluded as being compound-related. There was no compound-related effect on the type and the incidence of external, visceral, or skeletal malformations.

The following NOAELs were determined in this study:
Systemic maternal parameters: 100 mg/kg/day
Gestation rate: 100 mg/kg/day
Embryo/fetal development: 500 mg/kg/day

CONTAINS NO CBI

STUDY TITLE

MKH 6561
Developmental Toxicity Study in Rabbits
After Oral Administration

DATA REQUIREMENT

US EPA-FIFRA Guideline No. 83-3(b)

AUTHOR

Dr. B. Holzum

STUDY COMPLETION DATE

April 30, 1998

PERFORMING LABORATORY

BAYER AG
DEPARTMENT OF TOXICOLOGY
Friedrich-Ebert-Strasse 217-233
D-42096 Wuppertal
Germany

LABORATORY PROJECT ID

Bayer AG Report No. 27466
Bayer AG Study No. T0061724

STATEMENT OF DATA CONFIDENTIALITY

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10(d)(1)(A), (B), or (C):

BAYER CORPORATION

Dr. J.H. Thyssen: Gyesangha for J. H. Thyssen
Vice President, Toxicology

Date: Feb 1, 1999

GLP COMPLIANCE STATEMENT

This study was conducted in compliance with the OECD Principles of Good Laboratory Practice (GLP; German version published in: Bundesanzeiger No. 42a, March 2, 1983) and with the Principles of Good Laboratory Practice (GLP) according to Annex 1 ChemG (Bundesgesetzblatt Part I, July 29, 1994) and meets the FIFRA Good Laboratory Practice Standards (40 CFR Part 160), with the exception that recognized differences exist between the GLP principles/standards of OECD and FIFRA (for instance, authority granted Agency inspectors and certain record retention requirements).

B. Holzum

Dr. B. Holzum
Study Director

Febr. 3, 1998
Date

SPONSOR
BAYER AG

L. Machemer

Dr. L. Machemer

February 3, 1998
Date

SUBMITTER
BAYER CORPORATION

Gregaughen for J.H. Thyssen

Dr. J.H. Thyssen
Vice President, Toxicology

Feb 1, 1999
Date

FLAGGING STATEMENT

I have applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of the attached study. This study neither meets nor exceeds any of the applicable criteria.

SUBMITTER

BAYER CORPORATION

Dr. J.H. Thyssen: Gjesangha for J. H. Thyssen
Vice President, Toxicology

Date: Feb 1, 1999

SPONSOR

AGRICULTURE DIVISION

Dr. J.H. Thyssen: Gjesangha for J. H. Thyssen
Vice President, Toxicology

Date: Feb 1, 1999

Quality Assurance Statement

Test Item : MKH 6561

Study No.: T0061724

The study was audited by Quality Assurance on the dates given below. Audit reports have been submitted in writing to the study director and, if necessary, also to the laboratory management, or other persons affected.

Date of audit		Date of report to study director/ management
Aug. 06, 1997	(study plan)	Aug. 06, 1997
Aug. 14, 1997		Aug. 14, 1997
Sept. 18, 1997		Sept. 18, 1997
Oct. 21, 1997		Oct. 21, 1997
Nov. 06, 1997		Nov. 06, 1997

To the best of my knowledge, the results of the study and the methods used have been correctly reported.

Quality Assurance Unit
PH-QA-C/GLP, Bayer AG

Date: May 4, 1998 **Responsible:** Dr. H. Lehn

SIGNATURES

Study Director: B. Holzum April 30, 1998

Dr. B. Holzum Date

Head of Department: Eckhard von Keutz May 6, 1998

Dr. E. von Keutz Date

TABLE OF CONTENTS

1. SUMMARY

Twenty-two female Himalayan rabbits each were treated daily, orally by gavage, with MKH 6561 in 0.5 % carboxymethylcellulose from day 6 to 28 p.c. in doses of 0, 20, 100, 500 or 1000 mg/kg body weight/day, respectively. On day 29 of gestation the fetuses were delivered by cesarean section. Investigations were performed on general tolerance of the test compound by the females as well as on its effect on intrauterine development.

There was no indication of maternal toxicity at levels up to and including 100 mg/kg.

Doses of 500 and 1000 mg/kg resulted in symptoms (cold ears, alopecia, or swelling of vulva), abortions, decreased feed and water intakes and body weight loss. Furthermore, effects on the gastrointestinal tract (anal prolapse, diarrhea, light colored feces, solid contents in the stomach, enlarged cecum with gaseous contents or fluid, or light discoloration of the small intestine) occurred at levels of 500 and 1000 mg/kg as did effects on the liver (increased blood values for cholesterol, triglycerides, total bilirubin and GLDH, decreased protein levels in the blood, distinct lobulation or light discoloration of the liver, or decreased liver weight). Additionally, effects on the thyroid hormones (decreased T3 and T4 values, or increased thyroxine-binding capacity in the blood) were evident at the 500 and 1000 mg/kg levels.

In the 500 mg/kg group some of these effects were limited to the single female which revealed abortion (see below) while all females were affected in the 1000 mg/kg group.

There was no effect on intrauterine development at levels up to and including 100 mg/kg.

The gestation rate was marginally decreased by one abortion at the 500 mg/kg level and severely decreased by 18 abortions at the 1000 mg/kg level. These

abortions were most likely due to systemic maternal toxicity rather than a specific effect on reproduction.

The placental weights were distinctly decreased and the placentas were coarse grained and pale at the 1000 mg/kg level. The postimplantation loss in the females with viable fetuses was slightly increased and correspondingly the number of fetuses was slightly decreased at the 1000 mg/kg level. The fetal sex distribution was unaffected at levels up to and including 1000 mg/kg. The fetal weight was severely decreased and correspondingly skeletal ossification was retarded at the 1000 mg/kg level. Furthermore, an increased incidence of fetuses with distinct lobulation of the liver (variation) could not be excluded at the 1000 mg/kg level. The type and the incidence of external, visceral or skeletal malformations were unaffected at levels up to and including 1000 mg/kg.

The following no-observed-adverse-effect levels (NOAEL) were thus determined in this study:

Systemic maternal parameters:	100 mg/kg body weight/day
Gestation rate:	100 mg/kg body weight/day
Embryo/fetal development:	500 mg/kg body weight/day

2. INTRODUCTION

MKH 6561, a test compound with herbicidal properties, was tested for potential maternal and developmental effects in pregnant rabbits after oral administration.
The investigations were carried out at the Department of Toxicology Pharma of the Institute of Toxicology, BAYER AG, D-42096 Wuppertal, Friedrich-Ebert-Straße 217 - 333, Germany.
Clinical chemistry and hemostaseology were performed at the Department of Toxicologic Pathology of the Institute of Toxicology, BAYER AG.

Study initiation date:	August 4, 1997
Experimental starting date:	August 14, 1997
Experimental completion date:	November 18, 1997
Study completion date:	see signatures (page 6)

3. STUDY IDENTIFICATION AND RESPONSIBILITIES

3.1. Study Identification Number

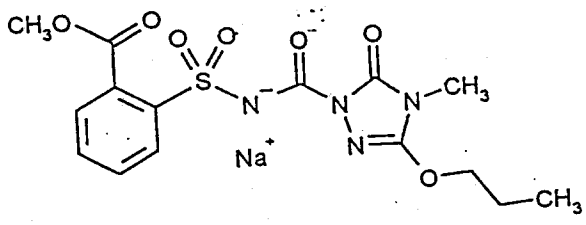
The study was allocated the study no. T0061724.

3.2. Personnel and Responsibilities

Head of Department:	Dr. E. von Keutz
Study Director:	Dr. B. Holzum
Clinical Chemistry, Hemostaseology:	Dr. I. Loof
Active Ingredient Analysis of the Test Compound:	Dr. W. Gau
Active Ingredient Analyses in the Administration Formulations:	Dr. W. Rüngeler
Quality Assurance:	Dr. H. Lehn
Archiving:	Prof. Dr. G. Schlüter Dr. M. Rosenbruch (fetuses)

4. MATERIALS AND METHODS

4.1. Test Compound and Administration Formulations

Test Compound:	MKH 6561
Common Name:	-
Manufacturer:	BAYER AG
Mixed Batch No.:	05649/0004
Development-No.:	0142835
Active Ingredient:	98.1 % (see page 398 in the Annex)
Approved for Use:	until December 27, 1997 (see page 398 in the Annex)
Appearance:	white powder
Storage Conditions:	at room temperature
Chemical Name (C.A.):	Benzoic acid, 2-[[[(4,5-dihydro-4-methyl-5-oxo-3-propoxy-1H-1,2,4-triazol-1-yl)carbonyl]amino] sulfonyl]-, methyl ester, sodium salt
CAS Registry No.:	181274-15-7
Structural Formula:	
Molar Mass:	420.4 g/mol
Empirical Formula:	$C_{15}H_{17}N_4NaO_7S$

For treatment of the animals, administration formulations were prepared using a suspension of 0.5 % carboxymethylcellulose (carboxymethylcellulose sodium salt high viscosity, Fluka Chemie AG, CH-9471 Buchs, Switzerland) in demineralized water, which has no effect on the investigated parameters. Fresh formulations for each concentration were prepared after two to at maximum eight days of use. The administration formulations were kept at room temperature for the duration of their use.

Investigations on the homogeneity and stability after 8 days storage of the active ingredient in samples with concentrations of 4 mg/ml and 100 mg/ml covering the concentrations used for the 20, 100 and 500 mg/kg groups had been performed before the start of study during study T8054289. Investigations on the homogeneity and stability after 8 days storage in an administration formulation containing 200 mg/ml were performed before start of treatment of the animals of the 1000 mg/kg group which was added to the study. Homogeneity and stability were confirmed in these investigations (see Annex, pages 399 - 403).

Content checks of the formulations for the 20, 100 and 500 mg/kg groups were carried out on September 2 and 29, 1997. Content checks of the formulation for the 1000 mg/kg group were performed on October 15 and 27, 1997. The results revealed no meaningful deviation of the active ingredient content from the nominal value in the formulations of any of the four treatment groups (see Annex, pages 404 - 409).

4.2. Testing Guidelines

This study was conducted in compliance with OECD guidelines (Guidelines for Testing of Chemicals, Section 4: Health Effects No. 414 "Teratogenicity", adopted May 12, 1981) and EEC guidelines (Commission Directive 88/302/EEC, Official Journal of the European Communities L 133, dated May 30, 1988) as well as US-EPA guidelines (Health Effects Test Guidelines, OPPTS 870.3700 "Prenatal Developmental Toxicity Study - Public Draft", EPA 712-C-96-207, dated February 1996) and Japanese MAFF guidelines (Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration, Requirements for Safety Evaluation of Agricultural Chemicals, "Teratogenicity Study", dated January 28, 1985).

4.3. Experimental Animals and Housing Conditions

4.3.1. Experimental Animals

This study was carried out in rabbits, a species recommended in testing guidelines for developmental toxicity studies. The female rabbits used were of the strain CHBB:HM, bred by Dr. Karl Thomae GmbH, Biberach. Himalayan rabbits of the CHBB:HM strain have been used at BAYER AG in developmental toxicity studies for years. Historical data are available for the investigated parameters. As can be seen from the historical data on the fertility and gestation rates (see pages 452 - 454 in the Annex) animals of this strain have been shown to exhibit a level of fertility sufficiently high for developmental toxicity studies. This strain exhibits good sensitivity to embryotoxic substances (1, 2).

After their arrival (June 11, July 10, August 7, September 11 and October 9, 1997) the females for this study were acclimatized to the conditions in the animal room until mating (at least 7 days), during which time they were thoroughly observed for signs of diseases. The animals had only been vaccinated against rabbit hemorrhagic disease. None of the animals was treated with antiinfectives. Only healthy animals, free of clinical signs, were used in this study. The females were nulliparous and nonpregnant. At the time of the mating period the males were mature to breed. The females were between 98 and 247 days old and their body weights ranged from 2042 to 3132 g, on day 0 p.c.

4.3.2. Housing Conditions

During the acclimatization period and also during the study the animals were kept individually in Makrolon® cages with perforated cage sheets.
All animals of this study were accommodated in animal room 33 of building 510. Animals of one intravenous and one oral developmental toxicity study with different test compounds (T6061333 and T1061725) were accomodated in the same room from August 14 to September 4, 1997 or from October 23 to November 18, 1997, respectively. An influence on the performance and outcome of this study by the joint housing is excluded.

4.3.3. Conditions in the Animal Room

The animal room had a standardized climate:

Room temperature:	20 - 22 °C
Relative humidity:	50 - 70 %
Light/dark cycle:	artificial lighting, 12 hour light/dark cycle
Air change:	at least 10 times per hour

Occasional deviations from these standards, such as those occurring when the animal room was cleaned, had no noticeable influence on the housing of the animals.

4.3.4. Nutrition

During the acclimatization period and the study period the animals received a standard diet (Ssniff® rabbit diet K - Z, producer: Ssniff Spezialdiäten GmbH, Soest) and tap water, both offered ad libitum.

Feed was offered to the animals in racks, which were automatically refilled out of feed containers.
Water was offered in polycarbonate bottles holding 700 ml.
The nutritional composition and degree of contamination of the standard diet were routinely and randomly checked and analyzed (for feed specification see page 410 in the Annex). The tap water was of drinking-water quality (Statute on Drinking-Water and Water for Food Processing Factories of December 5, 1990 (BGBl. I page 2612)).
Records of the analyses conducted to monitor compliance with feed and water specifications have been filed at BAYER AG.

4.3.5. Identification of Experimental Animals

Cards on the cage showed the animal ID-number, test compound, dose, study number, and date of initiation of the study (day 0 of gestation). In addition, the animals had been marked by the breeder by a tattooing number in the inner side of the ear.

4.3.6. Cleaning and Disinfection

The animal room was cleaned daily, using a disinfectant (Tego 2000®) three times per week.
At study initiation the animals were placed into clean cages with clean racks and water bottles. All cage equipment was cleaned with hot water.
Cage sheets and water bottles were changed routinely.

4.4. Mating and Start of Gestation

The mating was performed between 7 and 10 o'clock a.m. One male rabbit was mated with one female rabbit under observation. About one hour after the first mating had occurred the same animals were mated again. A different male was used for the second mating of females nos. 3269 (20 mg/kg), 3218 (100 mg/kg) and 3398 (1000 mg/kg). It was recorded which female was mated with which male.
The day on which the copulation was observed was considered as day 0 of gestation.

4.5. Dose Levels, Experimental Groups and Dose Selection

The male animals were used for mating only and remained untreated.
After copulation, 88 females were allocated to 4 experimental groups according to a computer generated randomisation plan (random number generator from an HP Vectra PC, for randomisation list see Annex, pages 394 - 396). Each of the experimental groups consisted of 22 females. As the females of the high dose group (500 mg/kg) did not display distinct signs of maternal toxicity occurring in the live animal phase during the first weeks after start of study an additional high dose group (1000 mg/kg) with 22 females was added to the running study.
The animals were treated daily from day 6 to 28 p.c. between 7 and 12 o'clock a.m.
The animals were given the administration formulation orally by gavage (rubber gavage no. 18, Rüsch).
The animals in all experimental groups received a uniform dose volume of 5 ml/kg body weight/day. The dose volume was adjusted to the current body weight which was determined before each administration, daily from day 6 to 28 p.c.

The following doses (related to the test compound) were administered:

	mg/kg body weight/day	concentration in mg/ml
Group 1 (Control)	0	0
Group 2 (Low dose)	20	4
Group 3 (Medium dose)	100	20
Group 4 (High dose I)	500	100
Group 5 (High dose II)	1000	200

These dose levels of groups 2 to 4 were selected according to a pilot developmental toxicity study with MKH 6561 in rabbits after oral administration (T8060750, see Annex pages 392 - 393). Group 5 was added during the course of the study (see above).

4.6. Survey of Investigations Performed

4.6.1. General Tolerance of the Treatment by the Females

Evaluation of the general tolerance of the test compound by the females was based on appearance and behavior, feed and water intakes, appearance of excretory products, body weight development and mortality of the animals as well as on clinical chemistry, hemostaseology, gross pathological findings and organ weights.
On October 7, 1997 one cage rack had been accidentally unfastened from the wall over night. Thus, it was not possible to evaluate feed and water intakes as well as excretory products from four animals on that day (no. 3256 (0 mg/kg), no. 3266 (20 mg/kg), no. 3254 (100 mg/kg), no. 3255 (500 mg/kg)).

4.6.1.1. Appearance, Behavior, Feed and Water Intakes, Excretory Products and Mortality

From day 0 to 28 p.c. the females were inspected twice daily - once on weekends, on public holidays and on day 29 p.c. - and all findings were recorded. Attention was paid to disturbances in the rabbits' general condition (appearance, behavior) and alterations concerning their excretory products. The feed intakes of the animals were determined from the difference in weight between the feed offered and the feed not consumed for the following days of gestation: days 0 - 6, 6 - 11, 11 - 16, 16 - 21, 21 - 24 and 24 - 29 p.c.
Water intake was assessed by visual estimation of the quantities left over.

4.6.1.2. Body Weight Development

The body weight of the females was determined on day 0 p.c. and daily from day 6 to day 29 p.c. Corrected body weight gain was determined by subtracting the uterus weight on day 29 p.c. from the body weight gain from day 0 to 29 p.c.

4.6.1.3. Clinical Chemistry and Hemostaseology

Blood samples from the hindlimb veins were taken from the last 10 females undergoing cesarean section on day 29 p.c. in the 0, 20, 100 and 500 mg/kg groups. Blood samples from all females which aborted in the 1000 mg/kg group samples were taken after abortion was evident. If abortion occurred on a weekend blood samples were taken on the following Monday. Blood samples from the remaining females without abortion in the 1000 mg/kg group were taken on the day of cesarean section on day 29 p.c. The determinations of the following enzymes, substrates, proteins, hormones and hemostaseological parameters were performed according to the methods listed in the Annex on pages 411 - 412.

Enzymes:

ASAT (GOT)	Aspartate aminotransferase
ALAT (GPT)	Alanine aminotransferase
APh	Alkaline phosphatase
GLDH	Glutamate dehydrogenase
GGT	Gamma-glutamyltransferase

Substrates:

CHOL	Cholesterol
TRIGL	Triglycerides
BILI-t	Bilirubin total

Proteins:

PROT	Protein
ALBUMIN	Albumin

Hormones:

T3	Triiodothyronine
T4	Thyroxine
TBC	Thyroxine-binding capacity

Hemostaseology:

PT/TPZ	Prothrombin time

4.6.1.4. Gross Pathological Investigations and Organ Weights

The females were subjected to gross pathological evaluation at cesarean section on day 29 p.c. The females which aborted were necropsied after abortion was evident. If abortion occurred on a weekend the females of the 1000 mg/kg group (no. 3401, 3403, 3404, 3407, 3411, 3412, 3414) were necropsied on the following Monday. The females were sacrificed by the intravenous injection of 2 ml T 61® ad us. vet. (Hoechst AG).

The liver was weighed from the 10 last females undergoing cesarean section in the 0, 20, 100 and 500 mg/kg groups as well as from all females in the 1000 mg/kg group.

The right upper liver lobe together with the gallbladder, stomach and intestines as well as the thyroid of the 10 last females of the 0, 20, 100 and 500 mg/kg groups as well as of all females in the 1000 mg/kg group were fixed in a 10 % formaldehyde solution. Histopathology on these fixed specimens was not performed due to the overall results of the study.

4.6.2. Investigations during Cesarean Section

For cesarean section the females were sacrificed on day 29 p.c. by the intravenous injection of 2 ml T 61® ad us. vet. (Hoechst AG) (see section 4.6.1.4. on page 26). The fetuses were killed on dry ice. During cesarean section the following data were ascertained and evaluated:

- number of corpora lutea and implantations (in animals without visible implantation sites after staining of the uterus with a solution of 10 % ammoniumsulfide (3))
- uterus weight (except from females with abortion in which the uterus weight was determined, but neither evaluated nor included into the report)
- individual weights and appearance of placentas
- number of live and dead fetuses
- number of early resorptions (only implantation site visible), late resorptions (fetal or placental remnant visible) and dead fetuses (fetuses without signs of life but without maceration)
- sex of all live fetuses
- individual weights of live fetuses
- occurrence of external findings in the fetuses
- occurrence of findings in abdominal, pelvic and thoracic organs and in the brain of the fetuses
  The fetuses were eviscerated according to the modified STAPLES technique (4), including a transverse section through the brain in about 50 % of the fetuses. After evaluation of the fetuses the viscera were discarded.
- occurrence of findings of the skeletal system including the cartilaginous part in the fetuses (processing and evaluation were performed after cesarean section)
  Staining of the cartilage of fetuses (including about 50 % of the skulls) was performed by using alcian blue (method described by INOUYE, modified (5)).

Afterwards the fetuses were cleared with diluted potassium hydroxide solution and were stained with alizarin red S according to the modified DAWSON technique (6).

- occurrence of visceral findings in the fetal skull
(evaluation of about 50 % of the fetal skulls according to the modified WILSON technique (7-8); processing and evaluation were performed after cesarean section)

The fetal evaluation followed standardized methods (9) which had been modified for evaluation of rabbit fetuses.

The following list gives an overview of the numbers of fetuses/skulls which were examined according to the above-mentioned methods:

Dose (mg/kg b.w./day)	Total number of fetuses	Preparation of skulls	
		skeletal	visceral
0	146	77	69
20	145	76	69
100	150	80	70
500	110	59	51
1000	10	5	5

4.7. Statistics

Females without implantation sites as well as females which aborted were with one exception (clinical chemistry, hemostaseology) not taken into account for calculation of mean values. Females with total resorption were not taken into account for calculation of group mean values of body weights, body weight gains, feed intakes, organ weights and of data of clinical chemistry and hemostaseology.
The mean values in the tables calculated by computer are the rounded results of the calculations with unrounded raw data values.
Skeletal localizations with mechanical damage in single fetuses were excluded from the calculation of percentages of affected localizations. The tables of individual skeletal findings enumerate those findings for which the affected localizations were excluded from calculation.

Differences between the control and MKH 6561-treated groups were considered significant when $p<0.05$. Statistical significance was tested using the following methods:

a. Analysis of Variance (ANOVA); in case of significances Dunnett's test for
   - feed intakes
   - body weights and body weight gains and corrected body weight gains
   - organ weights
   - number of corpora lutea per female
   - number of implantations per female
   - number of live fetuses per female and as percentage of implantations per female
   - placental weights
   - fetal weights

These calculations were performed using a Vax 4000/300 computer.

b. CHI^2 test (correction according to Yates) for
- fertility rate
- gestation rate
- number of fetuses or litters with malformations or with external or visceral deviations

These calculations were performed using a HP Vectra PC in case there were differences with respect to the control group.

c. 2 by N CHI^2 test; in case of significant differences Fisher's exact test with Bonferroni correction for
- number of implantations per group
- number of preimplantation losses per group
- number of postimplantation losses, early resorptions, late resorptions or dead fetuses per group
- number of live fetuses per group in percent of implantations
- number of male or female fetuses or fetuses with indeterminable sex per group
- number of fetuses or litters with skeletal findings

These calculations were performed using a Vax 4000/300 computer.

d. Kruskall-Wallis test; in case of significant differences Dunn's test for
- number of preimplantation losses per female
- number of postimplantation losses, early resorptions, late resorptions or dead fetuses per female
- number of male or female fetuses or fetuses with indeterminable sex per female

These calculations were performed using a Vax 4000/300 computer.

The statistical tests performed on parameters of clinical chemistry and hemostaseology are listed in the Annex, page 413.

4.8. Archiving

The study documents are archived in the document archives of the Institute of Toxicology. The fetuses and the fixed organs of the females are archived in the organ and tissue archives of the Department of Toxicologic Pathology of the Institute of Toxicology, BAYER AG, Wuppertal.

5. RESULTS

5.1. General Tolerance of the Treatment by the Females

5.1.1. Appearance, Behavior and Mortality

Appearance and behavior of the females were unaffected by treatment at levels up to and including 100 mg/kg.

One female of the 500 mg/kg group (no. 3252) aborted on day 29 p.c. and 18 females of the 1000 mg/kg group aborted between days 19 to 28 p.c. Although single abortions may occur spontaneously in the strain of rabbits used (see Historical control data in the Annex, pages 424 - 426) the abortion in one female of the 500 mg/kg group is considered treatment related due to the high incidence of abortions at the 1000 mg/kg level and as the affected female in the 500 mg/kg group had shown severely decreased feed intakes, decreased water intakes, diarrhea, distinct transient weight loss and cold ears, before. Furthermore, clinical chemistry and gross necropsy revealed distinct effects on the liver and effects on the thyroid hormones (see sections 5.1.2. to 5.1.5. on the following pages).

In addition to this female of the 500 mg/kg group all females of the 1000 mg/kg group showed cold ears starting between days 11 and 22 p.c.

An increased incidence of females with alopecia occurred at the 1000 mg/kg level which was considered treatment related. Alopecia which occurred in the lower dose groups is considered incidental as the number of affected females in these groups was within the normal incidence range for this finding (see Historical control data in the Annex, pages 424 - 426).

Sixteen females of the 1000 mg/kg group showed an anal prolapse for several days and one of these females additionally revealed swelling of the vulva for five days before abortion.

None of the animals died spontaneously.

An incidence table for the clinical findings as well as the individual animal data are given in the Annex on pages 63 - 64 and on pages 118 - 131.

5.1.2. Feed and Water Intakes and Excretory Products

The following Table 1 gives an overview on the feed intakes of the females with viable fetuses on day 29 p.c. Individual animal data for feed intakes including the females without successful pregnancy are given in the Annex on pages 132 - 136. Data on water intakes and excretory products may be found together with the other clinical findings in the Annex on pages 63 - 64 (incidence table) and 118 - 131 (individual data).

Table 1

Dose (mg/kg b.w./day)	0	20	100	500	1000
mean feed intakes (g/animal/day)					
day 0 - 6 p.c.:	89.1	88.4	87.3	84.8	87.8
day 6 - 11 p.c.:	84.5	81.8	81.0	66.9**	31.0**
day 11 - 16 p.c.:	76.3	71.9	67.4	61.0*	9.2**
day 16 - 21 p.c.:	89.3	83.8	85.9	73.9*	11.8**
day 21 - 24 p.c.:	83.3	81.6	86.8	78.9	16.7**
day 24 - 29 p.c.:	85.4	87.2	90.3	86.3	16.9**

* statistically significant difference to control $p < 0.05$

** statistically significant difference to control $p < 0.01$

As is evident from Table 1 the mean feed intakes of the females with viable fetuses were unaffected by treatment at levels up to and including 100 mg/kg.
The feed intakes of the females with viable fetuses were slightly, however statistically significantly, decreased from days 6 to 21 p.c. in the 500 mg/kg group and severely decreased during the whole treatment period in the 1000 mg/kg group. The female which aborted in the 500 mg/kg group (no. 3252) as well as all females which aborted in the 1000 mg/kg group also showed severely decreased feed intakes.

Correlating to these decreased feed intakes at the 500 and 1000 mg/kg levels the incidence of reduced feces was increased at these dose levels (500 mg/kg slightly). Furthermore, diarrhea occurred in the female which aborted in the 500 mg/kg group and in all females of the 1000 mg/kg group. Most of these females in the 1000 mg/kg group had shown soft feces before. Light colored feces occurred in three females of the 500 mg/kg group and in 14 females of the 1000 mg/kg group. As in most cases light colored feces occurred only transiently it is considered indicative of impaired digestion rather than of excretion of test compound which is a white powder.
Decreased water consumption combined with decreased urination occurred at higher incidences at the 500 mg/kg level when compared to the control group and in all females of the 1000 mg/kg group. Discoloration of urine (light yellow to red brown) indicative of urine concentration occurred in five females of the 500 mg/kg group and in all females of the 1000 mg/kg group. The slightly increased incidence of decreased water consumption at the 100 mg/kg level is considered incidental as the incidence of decreased urination and the number of females exhibiting this finding in this group did not differ to any meaningful extent from the control group values. The finding of discolored urine in three females of the 100 mg/kg group is also considered incidental as this finding only occurred for one or two days and as discoloration of urine may occur spontaneously in single animals as is evident from

the control group of this or of previous studies (see Historical control data in the Annex, page 424 - 426).
Reddish excretion occurred in one female of the 1000 mg/kg group two days before abortion.

5.1.3. Body Weight Development

The following Table 2 gives an overview of the body weight gains of the females with viable fetuses on day 29 p.c. during the treatment and gestation periods as well as of the corrected body weight gains. Individual data including the females without successful pregnancy are given in the Annex on pages 137 - 166.

Table 2

Dose	body weight gain (g)		
	mean		corrected
mg/kg b.w./day	day 6-29 p.c.	day 0-29 p.c.	day 0-29 p.c.
0	219.0	224.9	- 139.1
20	241.6	257.4	- 125.7
100	240.9	255.2	- 114.2
500	187.5	184.7	- 136.9
1000	- 154.5 **	- 95.5 **	-279.0

** statistically significant difference to control $p < 0.01$

As is evident from the above Table 2 the body weight gain of the females with viable fetuses on day 29 p.c. did not differ to any meaningful extent from the control

group value at levels up to and including 100 mg/kg body weight/day. The body weight gain during treatment and gestation in the 500 mg/kg group was marginally lower than in the control group. A statistically significant difference was, however, missing, and the corrected body weight gain in the 500 mg/kg group did not differ to any meaningful extent from the control group value, so that the lower weight gain in the 500 mg/kg group is considered the consequence of the incidentally slightly lower litter size (see Table 7 on page 45) rather than being indicative of maternal toxicity.

The females with viable fetuses in the 1000 mg/kg group showed distinct body weight loss during the treatment period and showed a decreased corrected weight gain also.

The females which aborted in the 500 mg/kg and 1000 mg/kg groups also showed weight loss (500 mg/kg distinct, however transient, 1000 mg/kg distinct, in some animals severe) between start of treatment and abortion.

5.1.4. Clinical Chemistry and Hemostaseology

Table 3 on the following page gives an overview on the mean values of the parameters of clinical chemistry and hemostaseology (enzymes, substrates, proteins, hormones, prothrombin time) determined in blood samples taken from the females with viable fetuses on 29 p.c. The individual values including the females without successful pregnancy are given in the Annex, on pages 167 - 170. Mean values on the females which aborted in the 1000 mg/kg group are listed in the Annex on page 75.

Table 3

Dose (mg/kg b.w./day)		0	20	100	500	1000
ASAT	(U/l)	19.7	19.2	18.7	16.4	12.6
ALAT	(U/l)	38.1	40.4	39.3	38.7	25.3
APh	(U/l)	78	72	66	63	52
GLDH	(U/l)	5.6	5.5	5.2	6.6	6.2
GGT	(U/l)	4	5	5	4	3
CHOL	(mmol/l)	0.29	0.29	0.29	0.29	0.80
TRIGL	(mmol/l)	0.35	0.29	0.33	0.29	0.40
BILI-t	(mcmol/l)	1.0	0.9	0.9	1.0	3.2
PROT	(g/l)	51.6	54.3	50.7	53.8	47.8
ALBUMIN	(g/l)	33.6	34.5	33.3	33.6	31.3
T3	(nmol/l)	1.67	1.76	1.76	1.59	0.38
T4	(nmol/l)	35	37	39	37	15
TBC	(TBI)	0.76	0.75	0.79	0.72	0.86
PT	(sec)	6.5	6.7	6.4	6.4	6.3

As is evident from the above Table 3 evaluation of clinical chemistry and hemostaseology parameters in the blood of the females with viable fetuses on day 29 p.c. did not reveal treatment related effects at levels up to and including 500 mg/kg.

The female which aborted on day 29 p.c. in the 500 mg/kg group (no. 3252) showed distinctly increased values for cholesterol, triglycerides and total bilirubin in the blood correlating to the macroscopic liver findings (light discoloration, distinct lobulation, see section 5.1.5. on page 39). Furthermore, this female showed slightly decreased albumin and total protein values in the blood most likely also due to

effects on the liver. Additionally decreased T3 and T4 values occurred in this female.

The two females with viable fetuses on day 29 p.c. in the 1000 mg/kg group also showed increased cholesterol and total bilirubin values as well as effects on the thyroid hormones (decreased T3 and T4, increased thyroxine-binding capacity). The mean total protein and albumin concentration was also slightly lower when compared to the control group, the individual values were however within the scattering range of the control group so that a treatment related effect on the blood protein status for these two animals is equivocal.

The evaluation of the clinical chemistry and hemostaseology data of the females which aborted in the 1000 mg/kg group has to take into consideration that abortion occurred at different timepoints of the gestation period (between days 19 to 28 p.c.) with different physiological values for the evaluated parameters (Historical control data for clinical chemistry and hemostaseology from earlier stages of pregnancy are included in the Annex, pages 434 - 447). Nevertheless, a distinct increase of cholesterol, triglycerides and total bilirubin and an increase of GLDH occurred in the blood of these animals. Furthermore, decreased T3 and T4 values and increased thyroxine-binding capacity were measured. (see Annex, page 75)

Thus, effects on the liver (increase in cholesterol and/or triglycerides and total bilirubin, increased GLDH values in the females with abortion of the 1000 mg/kg group, and/or decrease in proteins) as well as effects on the thyroid hormones (decreased T3 and T4 values and/or increased thyroxine-binding capacity) occurred in the females which aborted at the 500 and 1000 mg/kg levels and in the two females with successful pregnancy of the 1000 mg/kg group.

5.1.5. Gross Pathological Findings and Organ Weights

Necropsy of the animals did not reveal treatment related findings at levels up to and including 100 mg/kg.

The females of the 500 and 1000 mg/kg groups showed findings in the gastrointestinal tract and in the liver.

Enlarged cecum occurred in 11 females of the 500 mg/kg group and in all females of the 1000 mg/kg group. The females of the 1000 mg/kg group also showed changes in the cecal contents (gaseous contents, fluid). Furthermore, two females of the 1000 mg/kg group showed solid contents in the stomach and three further females showed light discoloration of the small intestine.

A treatment related effect for gaseous contents occurring in the rectum of three or two animals of the 500 and 1000 mg/kg groups is equivocal, as a dose dependency was missing and as two animals of the control group showed the same finding.

The female which aborted in the 500 mg/kg group (no. 3252) showed distinct lobulation and light discoloration of the liver. Two females in the 1000 mg/kg group also showed distinct liver lobulation.

The other necropsy findings did not indicate a treatment related effect as a dose dependency was missing, only single animals were affected, or the findings were morphological changes that must have already been present before the start of treatment.

The necropsy findings are listed in the Annex on pages 76 - 77 (incidence table) and 171 - 176 (individual data).

The following Table 4 gives an overview on the absolute and relative (related to carcass weights) liver weights of the females with viable fetuses on day 29 p.c. Individual data including the females without successful pregnancy are given in the Annex on pages 177 - 186.

Table 4

Dose	Liver weight	
	absolute	relative
mg/kg b.w./day	g	g/g
0	57.4	0.0249
20	55.6	0.0245
100	58.5	0.0260
500	59.0	0.0253
1000	43.9	0.0220

As is evident from the above Table 4 the liver weight of the females with viable fetuses on day 29 p.c. was unaffected by treatment at levels up to and including 500 mg/kg. The two females of the 1000 mg/kg group with viable fetuses on day 29 p.c. revealed a decreased absolute and relative liver weight. The females which aborted also showed a slightly decreased mean absolute liver weight (51.1 g).

5.2. General Reproduction Data

Table 5

Dose mg/kg b.w./day	0	20	100	500	1000
mated females	22	22	22	22	22
mated females evaluated	22	22	22	22	22
females with implantations	21	20	21	19	20
in % of those mated	95.5	90.9	95.5	86.4	90.9
mean values					
per female with implantations +					
corpora lutea	8.2	8.1	8.8	7.7	10.0
preimplantation loss	0.8	0.5	1.0	0.8	3.0
implantations	7.4	7.6	7.7	6.9	7.0

+ without females which aborted

The data in the above Table 5 show that the fertility rate (percentage of mated females with implantations) as well as the mean number of implantation sites did not differ to any meaningful extent in the different groups so that a homogenous distribution was given regarding these parameters.

The mean number of corpora lutea and the preimplantation loss in the two females with implantation sites in the 1000 mg/kg group which did not abort was higher when compared to the other groups including the control group. An impact on the outcome of the study is, however, excluded as the mean number of implantation sites in this group was similar to the control group value.

5.3. Effect of Test Compound on Intrauterine Development

5.3.1. Gestation Rate

The following Table 6 shows the gestation rate (percentage of females with viable fetuses on day 29 p.c. of those with implantation sites) in the different study groups.

Table 6

Dose	Females with viable fetuses on day 29 p.c.		abortion	total resorption
mg/kg b.w./day	n	in % of females with implantations	n	n
0	21	100.0	0	0
20	20	100.0	0	0
100	21	100.0	0	0
500	17	89.5	1	1
1000	2	10.0 ***	18	0

*** statistically significant difference to control $p < 0.001$

The gestation rate was unaffected by treatment at levels up to and including 100 mg/kg.

The gestation rate was marginally decreased at the 500 mg/kg level due to one female (no. 3249) with total resorption of all three implants (early resorptions) and due to one female (no. 3252) which showed abortion on day 29 p.c. Single females with total resorptions may occur spontaneously in the strain of rabbits used (see Historical control data and data from different study groups in the Annex, pages 455 - 458). Furthermore, there was no further indication of an increased rate of

early resorptions at the 500 mg/kg level and there was no female with complete early resorption in the 1000 mg/kg group. Therefore, the single total resorption, which occurred at the 500 mg/kg level, is considered unrelated to treatment. Although also abortions may occur spontaneously in the strain of rabbits used (see Historical control data in the Annex, pages 424 - 426) a treatment related effect is assumed for the single abortion in the 500 mg/kg group as the affected female showed further severe signs of maternal toxicity (see section 5.1.1. on page 32) and due to abortions at the 1000 mg/kg level.
The gestation rate was severely decreased in the 1000 mg/kg group by 18 abortions.

The mean values of the parameters of intrauterine development reported under section 5.3.2. to 5.3.5. along with the results of the statistical tests are contained in the following Table 7 and on pages 82 - 87 in the Annex. Individual data are given in the Annex on pages 190 - 295.
Due to the high number of abortions at the 1000 mg/kg level the data in this group are based on two females with viable fetuses only.

Table 7

Dose (mg/kg b.w./day)	0	20	100	500	1000
number of females +					
with implantations (a)	21	20	21	18	2
with viable fetuses (b)	21	20	21	17	2
mean values per female					
placental weight in g (b)	4.33	4.46	4.25	3.94	3.15
number of fetuses (b)	7.0	7.3	7.1	6.5	5.0
postimplantation loss (a)	0.5	0.3	0.6	0.8	2.0
postimplantation loss (b)	0.5	0.3	0.6	0.6	2.0
males in % (b)	50.0	50.8	49.9	55.5	50.0
fetal weight in g (b)	37.29	37.48	36.87	35.25	23.14 **

** statistically significant difference to control $p < 0.01$

\+ without females with abortion

5.3.2. Weight and Appearance of Placentas

The external appearance and weight of the placentas did not differ to any meaningful extent from those of the placentas in the control group and the placental weight lay within the range of historical control data (see Annex, page 460) at levels up to and including 500 mg/kg. The placental weights were distinctly decreased in the 1000 mg/kg group. Furthermore, all placentas of the two females with viable fetuses on day 29 p.c. in the 1000 mg/kg group were coarse grained and in one female additionally pale.

Individual placental observations and an incidence table are given in the Annex on pages 296 - 300 and on page 88.

5.3.3. Postimplantation Loss, Number of Fetuses

The postimplantation loss and correspondingly the number of fetuses in the females without abortion were unaffected by treatment at levels up to and including 500 mg/kg. The postimplantation loss was marginally increased by two late resorptions in each of the two females with viable fetuses on day 29 p.c. in the 1000 mg/kg group. Accordingly the number of fetuses was slightly decreased at the 1000 mg/kg level.

5.3.4. Sex of Fetuses

The percentage of male or female fetuses did not reveal a treatment related effect at levels of up to and including 1000 mg/kg.

5.3.5. Fetal Weight

The fetal weight was unaffected by treatment at levels up to and including 500 mg/kg. The marginally lower fetal weight at the 500 mg/kg level when compared to the control group value is considered incidental as a statistical significance was missing and as differences like between the control and 500 mg/kg group in this study may occur spontaneously within different study groups (see data from study T0058034 in the Annex, page 487).
The fetal weight was severely decreased at the 1000 mg/kg level.

5.3.6. Fetal Malformations

Table 8 on page 49 gives an overview on the external, visceral and skeletal malformations in the fetuses. The individual fetal data (malformations) are given in the Annex on pages 387 - 388.

The total incidences of fetuses or litters with malformations did not differ to any meaningful extent from the control group values at levels up to and including 1000 mg/kg.

The malformations in the dose groups were different in type, did not reveal a dose dependency and were comparable to findings in the control group of this study (malposition of forelimbs, malformation of ribs) or of previous developmental toxicity studies in the same laboratory with the same strain of rabbits (cardiac septal defect with malposition of major vessels, supernumerary vertebra with supernumerary pair of ribs, combined malformation of thoracic vertebrae and ribs, missing lumbar vertebra or fusion of caudal vertebral bodies, see Historical control data in the Annex, pages 495 - 504).

The only finding which occurred at a slightly higher fetal incidence in one of the groups treated with MKH 6561 (100 mg/kg) was malposition of forelimbs (hyperflexion at the region of the wrist). Malposition of forelimbs is the most common spontaneous malformation in the strain of rabbits used (see Historical data in the Annex, pages 495 - 504, referred to as arthrogryposis in the tables covering the period until 1994) and is most likely due to restriction of fetal movement in the uterus (10). The percentage of affected fetuses (3.3 %, litter incidence 19.0 %) lay below the percentage of fetuses with the same finding (5.6 %, litter incidence 31.3 %) in the control group of an oral developmental toxicity study in rabbits which was performed in the same year in the same laboratory (T5061099), and no such finding occurred at the 500 mg/kg level.

Thus, there is no indication that treatment with MKH 6561 might have affected the incidence or the type of malformations at levels up to and including 1000 mg/kg.

Table 8

Malformation	Dose (mg/kg b.w./day) 0	20	100	500	1000
malposition of forelimb(s)	3 (3)	2 (1)	5 (4)		
cardiac ventricular septal defect with malposition of ascending aorta			1		
fusion/bifurcation of ribs in the cartilaginous part	2 (2)		1		
supernumerary thoracic vertebra with 13th ribs		1	1		
combined malformation of thoracic vertebrae and ribs				1	
missing lumbar vertebra		1			
fusion of caudal vertebral bodies		2 (2)			
number of fetuses per group	146	145	150	110	10
number of fetuses with malf.	5	6	7	1	0
fetuses with malf. per group (%)	3.4	4.1	4.7	0.9	0
number of litters per group	21	20	21	17	2
number of litters with malf.	5	5	6	1	0
litters with malf. per group (%)	23.8	25.0	28.6	5.9	0

() number of litters affected

As one fetus of the 100 mg/kg group revealed more than one malformation the total number of malformations is higher than the number of affected fetuses in this group.

5.3.7. Fetal External and Visceral Deviations

The following Table 9 gives an overview of external and visceral deviations (findings other than malformations) in the fetuses. Individual data are listed in the Annex on pages 389 - 391.

Table 9

Deviation	Dose (mg/kg b.w./day) 0	20	100	500	1000
cyst at the palate		1			
accumulation of fluid in the abdominal cavity			1		
accessory liver lobe				1	
distinct liver lobulation	17 (4)	22 (5)	5** (2)	12 (2)	4 (1)
glassy vesicles on the liver			1		
dilation of renal pelvis		1			
number of fetuses per group	146	145	150	110	10
number of fetuses with deviat.	17	24	6**	13	4
fetuses with deviat. per group (%)	11.6	16.6	4.0	11.8	40.0
number of litters per group	21	20	21	17	2
number of litters with deviat.	4	6	3	3	1
litters with deviat. per group (%)	19.0	30.0	14.3	17.6	50.0

*** statistically significant difference to control $p < 0.001$
() number of litters affected

As one fetus of the 100 mg/kg group revealed more than one deviation the total number of deviations is higher than the number of affected fetuses in this group.

As is evident from Table 9 on the previous page the overall percentage of fetuses or litters with external or visceral deviations was not dose dependently affected at levels up to and including 500 mg/kg. Except from distinct liver lobulation which also occurred in several fetuses of the control group the findings occurred in single fetuses only, were different in type and were comparable to spontaneous findings in previous developmental toxicity studies in the same strain of rabbits used except from cyst at the palate and dilation of renal pelvis (see Historical control data and data from different study groups in the Annex, pages 505 - 508). Thus, there is no indication that treatment with MKH 6561 might have caused external or visceral deviations at levels up to and including 500 mg/kg.
All fetuses of one of the two females with viable fetuses in the 1000 mg/kg group revealed distinct liver lobulation. Due to the low number of 10 fetuses only in this group a final evaluation of this finding is not possible.

5.3.8. Fetal Skeletal Deviations

Fetal examination for skeletal retardations and variations did not reveal meaningful differences between the control group and the groups treated with MKH 6561 at levels up to and including 500 mg/kg. There were only three statistically significant differences in these groups when calculation was done on a fetal basis while calculation on a litter basis did not reveal any statistical significant differences at levels up to and including 500 mg/kg. The statistically significant differences on a fetal basis in the 100 mg/kg group (first cervical vertebral body) and 500 mg/kg group (right and left 8th caudal vertebral arches) were indicative of advanced ossification in these locations. The values were within the normal scattering range (see Historical control data in the Annex, pages 511 - 526) and did not show a dose dependency. Single fetuses revealed cervical ribs at the 100 mg/kg (two fetuses) and 500 mg/kg (one fetus) levels. A dose dependency was, however, not given and

it is evident from the historical control data in the Annex on pages 511 - 526 that cervical ribs may occur spontaneously in the strain of rabbits used.
Skeletal ossification was retarded in the fetuses of the 1000 mg/kg group. Statistically significant differences occurred in the phalanges of fore and hindlimbs, in the metarcarpals and caudal vertebral bodies as well as in the skull (enlarged fontanelle). This incomplete ossification correlated with the severely decreased fetal weights in this group (see section 5.3.5. on page 47).

The skeletal findings are listed in the Annex on pages 94 - 115 (incidence tables) and pages 312 - 386 (individual data).
The criteria for classifying the observed skeletal findings as deviations (variations, retardations) or malformations are shown in the Annex on pages 414 - 418.

6. EVALUATION

Twenty-two female Himalayan rabbits each were treated daily, orally by gavage, with MKH 6561 in 0.5 % carboxymethylcellulose from day 6 to 28 p.c. in doses of 0, 20, 100, 500 or 1000 mg/kg body weight/day, respectively. On day 29 of gestation the fetuses were delivered by cesarean section. Investigations were performed on general tolerance of the test compound by the females as well as on its effect on intrauterine development.

Toxicity to the Females

One female of the 500 mg/kg group aborted on day 29 p.c and 18 females of the 1000 mg/kg group aborted between days 19 to 28 p.c. These females had shown severe signs of systemic toxicity before (see below).

The female which aborted in the 500 mg/kg group and all females of the 1000 mg/kg group showed cold ears. Furthermore, an increased incidence of alopecia occurred in the females of the 1000 mg/kg group. Additionally, 16 females of the 1000 mg/kg group showed an anal prolapse for several days and one of these females additionally showed swelling of the vulva before abortion.

None of the females died spontaneously.

The feed intakes of the females with viable fetuses in the 500 mg/kg group were slightly decreased from days 6 to 21 p.c. and were severely decreased in the female which aborted in the 500 mg/kg group and in all females of the 1000 mg/kg group. Correspondingly the amount of feces was reduced at levels of 500 mg/kg and above (500 mg/kg slightly). Diarrhea occurred in the female which aborted in the 500 mg/kg group and in all females of the 1000 mg/kg group. Light colored feces occurred in 3 females of the 500 mg/kg group and in 14 females of the 1000 mg/kg group. Decreased water consumption and decreased and thus concentrated and discolored urination occurred at levels of 500 mg/kg and above.

The female which aborted in the 500 mg/kg group showed distinct transient weight loss and all females in the 1000 mg/kg group showed distinct to severe weight loss between start of treatment and abortion.

Clinical chemistry in the blood revealed the following findings in the female which aborted in the 500 mg/kg group and in all females of the 1000 mg/kg group: distinctly increased values for cholesterol or triglycerides, total bilirubin, GLDH (only in females with abortion in the 1000 mg/kg group), decreased protein levels (equivocal in the females with viable fetuses, not evident in the females with abortion in the 1000 mg/kg group), decreased T3 and T4 values as well as an increased thyroxine-binding capacity (1000 mg/kg only).

The hemosteological parameter prothrombin time was unaffected by treatment at levels up to and including 1000 mg/kg.

Gross necropsy of the females revealed findings in the gastrointestinal tract in 11 females of the 500 mg/kg group and in all females of the 1000 mg/kg group (enlarged cecum, possibly gaseous contents in the rectum, 1000 mg/kg only: solid contents in the stomach, gaseous contents or fluid in the cecum, light discoloration of the small intestine). Furthermore, distinct lobulation or light discoloration of the liver occurred in the female which aborted in the 500 mg/kg group and in two females of the 1000 mg/kg group. The liver weight was decreased at the 1000 mg/kg level.

Thus, there was no indication of maternal toxicity at levels up to and including 100 mg/kg. Doses of 500 and 1000 mg/kg resulted in symptoms (cold ears, alopecia, swelling of vulva), abortions, decreased feed and water intakes and body weight loss. Furthermore, effects on the gastrointestinal tract (anal prolapse, diarrhea, light colored feces, solid contents in the stomach, enlarged cecum with gaseous contents or fluid, light discoloration of the small intestine) occurred at levels of 500 and 1000 mg/kg as did effects on the liver (increased blood values for cholesterol, triglycerides, total bilirubin and GLDH, decreased protein levels in the blood, distinct lobulation or light discoloration of the liver, decreased liver weight).

Additionally, effects on the thyroid hormones (decreased T3 and T4 values, increased thyroxine-binding capacity in the blood) were evident at the 500 and 1000 mg/kg levels.

Toxicity to Intrauterine Development

With respect to intrauterine development the gestation rate was marginally decreased by one abortion at the 500 mg/kg level and severely decreased by 18 abortions (out of 20 females with implantation sites) at the 1000 mg/kg level. These abortions were most likely due to systemic maternal toxicity (see above) rather than a specific effect on reproduction. Due to the high number of abortions at the 1000 mg/kg level the evaluation of fetal parameters was limited to two females in this group.

The placental weights were distinctly decreased and the placentas were coarse grained and pale at the 1000 mg/kg level. The postimplantation loss in the females with viable fetuses was slightly increased and correspondingly the number of fetuses was slightly decreased at the 1000 mg/kg level. The fetal sex distribution was unaffected at levels up to and including 1000 mg/kg. The fetal weight was severely decreased and correspondingly skeletal ossification was retarded at the 1000 mg/kg level. Furthermore, an increased incidence of fetuses with distinct lobulation of the liver, which is a common variation in the strain of rabbits used, could not be excluded at the 1000 mg/kg level. The type and the incidence of external, visceral or skeletal malformations were unaffected at levels up to and including 1000 mg/kg.

Thus, intrauterine development was unaffected by treatment at levels up to and including 100 mg/kg.

The gestation rate was decreased by abortions at levels of 500 mg/kg and above.

Embryo/fetal development was only affected at the 1000 mg/kg level indicated by a retarded development (decreased weights, retarded skeletal ossification) and

possibly an increased incidence of variations (distinct lobulation of the liver). A teratogenic potential of MKH 6561 was not evident.

Conclusion

The following no-observed-adverse-effect levels (NOAEL) were determined in this study:

Systemic maternal parameters:	100 mg/kg body weight/day
Gestation rate:	100 mg/kg body weight/day
Embryo/fetal development:	500 mg/kg body weight/day

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(7) On the Evaluation of the Fetuses in Teratological Experiments. Modification of the "Wilson technique".

(9) Embryotoxic Effects in the Rat.

8. LIST OF ABBREVIATIONS

a.m.	ante meridiem
ad us. vet.	ad usum veterinarium
Anim.	animal
B.w.; b.w.	body weight
CET	Central European Time
D	diameter
E	excluded from calculation of mean values
deviat.	deviations
malf.	malformations
nc	not calculated
NO.; no.; N; n	number
P.C.; p.c.	post coitum
p.m.	post meridiem
p.o.	per os
RAND-NO (NR)	random number
S.D. ; SD; st. dev.;	standard deviation
$\bar{x}$	mean value

In the lists of "Individual female reproduction data with individual fetal data" the fixation codes s = skeletal and v = visceral refer to the fetal skulls, only.

9. ANNEX: Tables of clinical and gross pathological findings, feed intakes, body weights and body weight gains, data of clinical chemistry and hemostaseology, organ weights, data of intrauterine development, results of the pilot study, randomisation list, data on active ingredient analyses, composition of feed, classification scheme of fetal skeletal findings and historical control data

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MKH 6561

SUMMARY OF CLINICAL OBSERVATIONS DURING GESTATION (FREQUENCY/ANIMALS)

	0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAY 0 to 5					
NORMAL					
NO REMARKABLE CLINICAL OBSERVATIONS	125/17	120/12	123/18	114/11	123/15
EXCRETION					
INCREASED URINATION	0/ 0	6/ 5	6/ 3	6/ 5	5/ 4
REDUCED FECES	4/ 2	0/ 0	0/ 0	2/ 1	0/ 0
DECREASED URINATION	1/ 1	2/ 2	1/ 1	1/ 1	1/ 1
DISCOLORED URINATION (LIGHT YELLOW)	0/ 0	0/ 0	0/ 0	2/ 1	0/ 0
SOFT FECES	0/ 0	0/ 0	1/ 1	0/ 0	1/ 1
MISCELLANEOUS					
INCREASED WATER CONSUMPTION	1/ 1	8/ 7	5/ 1	13/ 8	4/ 4
DECREASED WATER CONSUMPTION	4/ 3	1/ 1	1/ 1	0/ 0	0/ 0

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MKH 6561

SUMMARY OF CLINICAL OBSERVATIONS DURING GESTATION (FREQUENCY/ANIMALS)

	0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAY 6 to 29					
NORMAL					
NO REMARKABLE CLINICAL OBSERVATIONS	412/ 1	408/ 0	346/ 0	311/ 0	36/ 0
DEAD					
KILLED BECAUSE OF ABORTION	0/ 0	0/ 0	0/ 0	1/ 1	18/18
SKIN/FUR					
ALOPECIA	0/ 0	9/ 2	20/ 2	34/ 3	54/ 7
SCRATCHES, SWELLING	15/ 1	0/ 0	0/ 0	0/ 0	0/ 0
COLD TO TOUCH (EARS)	0/ 0	0/ 0	0/ 0	6/ 1	229/22
WOUND	0/ 0	5/ 1	0/ 0	0/ 0	0/ 0
EXCRETION					
INCREASED URINATION	39/10	36/ 7	50/10	27/13	10/ 6
REDUCED FECES	10/ 5	8/ 4	24/ 6	43/ 7	349/22
DECREASED URINATION	44/15	46/13	65/15	106/15	260/22
DISCOLORED URINATION (LIGHT YELLOW)	2/ 1	2/ 2	1/ 1	13/ 1	216/22
LIGHT COLORED FECES	0/ 0	0/ 0	0/ 0	6/ 3	51/14
SOFT FECES	0/ 0	0/ 0	1/ 1	1/ 1	56/16
DISCOLORED URINATION (RED BROWN)	0/ 0	0/ 0	4/ 2	14/ 4	3/ 1
NO FECES	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
DIARRHEA	0/ 0	0/ 0	0/ 0	3/ 1	172/22
ABORTION	0/ 0	0/ 0	0/ 0	1/ 1	18/18
REDDISH EXCRETION	0/ 0	0/ 0	0/ 0	0/ 0	2/ 1
EXCRETION NOT EVALUATED	1/ 1	1/ 1	1/ 1	1/ 1	0/ 0
DISCOLORED URINATION (REDDISH)	0/ 0	0/ 0	0/ 0	0/ 0	6/ 4
MISCELLANEOUS					
INCREASED WATER CONSUMPTION	28/ 9	42/10	60/15	52/13	3/ 3
DECREASED WATER CONSUMPTION	10/ 4	13/ 9	29/11	54/ 9	269/22
WATER CONSUMPTION NOT EVALUATED	1/ 1	1/ 1	1/ 1	1/ 1	0/ 0
ANAL PROLAPSE	0/ 0	0/ 0	0/ 0	0/ 0	87/16
SWELLING OF VULVA	0/ 0	0/ 0	0/ 0	0/ 0	6/ 1

MEAN FEED CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAYS 0 TO 6	MEAN	89.14 d	88.43	87.34	84.78	87.83
	S.D.	12.172	12.840	10.641	15.338	4.478
	N	21	20	21	17	2
	p-value	0.869				
DAYS 6 TO 11	MEAN	84.53 d	81.83	81.04	66.85**	31.00**
	S.D.	16.999	18.106	16.666	13.730	1.414
	N	21	20	21	17	2
	p-value	0.000	0.959	0.898	0.006	0.000
DAYS 11 TO 16	MEAN	76.31 d	71.89	67.43	60.99*	9.20**
	S.D.	16.345	16.455	19.127	16.718	5.091
	N	21	20	21	17	2
	p-value	0.000	0.827	0.278	0.027	0.000
DAYS 16 TO 21	MEAN	89.34 d	83.79	85.87	73.85*	11.80**
	S.D.	17.653	17.346	18.618	15.075	7.071
	N	21	20	21	17	2
	p-value	0.000	0.694	0.913	0.026	0.000
DAYS 21 TO 24	MEAN	83.29 d	81.61	86.81	78.88	16.67**
	S.D.	9.371	14.058	12.712	10.763	15.085
	N	21	19	21	17	2
	p-value	0.000	0.978	0.740	0.633	0.000
DAYS 24 TO 29	MEAN	85.38 d	87.23	90.30	86.26	16.90**
	S.D.	13.070	12.207	11.091	10.350	13.718
	N	20	20	20	16	2
	p-value	0.000	0.966	0.491	0.998	0.000

Statistical key: d=Dunnett's-test * = p<0.05 ** = p<0.01

MEAN BODY WEIGHTS DURING GESTATION (GRAMS)

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAY 0	MEAN	2497.6 d	2472.3	2422.7	2517.8	2266.5
	S.D.	207.54	256.62	202.84	214.91	212.84
	N	21	20	21	17	2
	p-value	0.443				
DAY 6	MEAN	2503.5 d	2488.1	2437.0	2515.1	2325.5
	S.D.	183.19	223.90	172.07	188.61	167.58
	N	21	20	21	17	2
	p-value	0.521				
DAY 7	MEAN	2495.0 d	2487.5	2428.5	2510.1	2312.5
	S.D.	190.48	221.93	176.02	194.37	125.16
	N	21	20	21	17	2
	p-value	0.495				
DAY 8	MEAN	2492.2 d	2484.4	2423.2	2507.9	2295.0
	S.D.	187.36	216.17	172.11	194.32	115.97
	N	21	20	21	17	2
	p-value	0.418				
DAY 9	MEAN	2493.3 d	2480.6	2426.4	2503.0	2293.0
	S.D.	179.82	218.77	170.34	197.33	114.55
	N	21	20	21	17	2
	p-value	0.455				
DAY 10	MEAN	2498.5 d	2477.1	2433.3	2501.9	2283.0
	S.D.	178.79	212.86	171.44	203.22	151.32
	N	21	20	21	17	2
	p-value	0.460				
DAY 11	MEAN	2494.8 d	2490.4	2429.0	2511.2	2265.5
	S.D.	167.21	210.67	171.15	199.07	125.16
	N	21	20	21	17	2
	p-value	0.316				
DAY 12	MEAN	2494.6 d	2484.6	2432.0	2501.9	2256.5
	S.D.	172.76	201.97	172.54	199.10	147.78
	N	21	20	21	17	2
	p-value	0.350				
DAY 13	MEAN	2507.0 d	2500.1	2434.7	2512.0	2223.0
	S.D.	174.77	199.93	163.56	192.93	171.12
	N	21	20	21	17	2
	p-value	0.177				
DAY 14	MEAN	2520.9 d	2507.3	2445.0	2525.2	2233.0
	S.D.	170.22	189.27	169.14	197.04	166.88
	N	21	20	21	17	2
	p-value	0.160				
DAY 15	MEAN	2539.9 d	2529.8	2467.8	2539.9	2219.0
	S.D.	164.85	189.74	170.08	196.75	155.56
	N	21	20	21	17	2
	p-value	0.114				

Statistical key: d=Dunnett's-test

MEAN BODY WEIGHTS DURING GESTATION (GRAMS)

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAY 16	MEAN	2561.1 d	2543.2	2485.0	2553.9	2215.0
	S.D.	160.37	184.34	169.04	200.75	169.71
	N	21	20	21	17	2
	p-value	0.081				
DAY 17	MEAN	2575.5 d	2553.1	2493.1	2555.2	2233.5
	S.D.	156.24	180.15	168.83	190.31	135.06
	N	21	20	21	17	2
	p-value	0.074				
DAY 18	MEAN	2573.5 d	2554.1	2490.4	2550.4	2215.5
	S.D.	160.72	178.46	170.74	184.91	135.06
	N	21	20	21	17	2
	p-value	0.056				
DAY 19	MEAN	2569.5 d	2557.9	2494.8	2568.0	2211.0
	S.D.	160.67	180.65	173.41	187.11	110.31
	N	21	20	21	17	2
	p-value	0.054				
DAY 20	MEAN	2570.5 d	2563.9	2495.7	2560.1	2193.0*
	S.D.	161.62	177.62	164.45	183.11	113.14
	N	21	20	21	17	2
	p-value	0.034	1.000	0.423	0.999	0.015
DAY 21	MEAN	2574.9 d	2563.8	2499.5	2570.4	2189.0*
	S.D.	160.57	170.37	165.96	183.19	94.75
	N	21	20	21	17	2
	p-value	0.026	0.999	0.407	1.000	0.011
DAY 22	MEAN	2586.9 d	2579.8	2515.7	2578.8	2196.0**
	S.D.	159.39	167.96	170.42	180.73	83.44
	N	21	20	21	17	2
	p-value	0.026	1.000	0.455	1.000	0.010
DAY 23	MEAN	2595.9 d	2593.9	2535.8	2594.0	2203.0*
	S.D.	161.53	169.48	170.10	188.92	53.74
	N	21	20	21	17	2
	p-value	0.031	1.000	0.614	1.000	0.011
DAY 24	MEAN	2613.3 d	2616.5	2557.0	2604.2	2198.0**
	S.D.	158.35	169.43	167.16	187.72	67.88
	N	21	20	21	17	2
	p-value	0.019	1.000	0.656	1.000	0.006
DAY 25	MEAN	2645.5 d	2643.1	2582.8	2629.4	2216.5**
	S.D.	159.59	165.17	168.66	185.36	57.27
	N	21	20	21	17	2
	p-value	0.014	1.000	0.564	0.995	0.004
DAY 26	MEAN	2658.5 d	2660.9	2609.0	2645.5	2226.0**
	S.D.	164.39	162.41	172.14	189.81	53.74
	N	21	20	21	17	2
	p-value	0.017	1.000	0.752	0.998	0.004

Statistical key: d=Dunnett's-test * = p<0.05 ** = p<0.01

MEAN BODY WEIGHTS DURING GESTATION (GRAMS)

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAY 27	MEAN	2682.8 d	2682.4	2631.7	2664.5	2174.5**
	S.D.	167.11	172.33	173.26	182.04	108.19
	N	21	20	21	17	2
	p-value	0.004	1.000	0.740	0.993	0.001
DAY 28	MEAN	2696.7 d	2701.1	2645.1	2676.2	2179.0**
	S.D.	162.24	163.34	175.47	184.39	113.14
	N	21	20	21	17	2
	p-value	0.002	1.000	0.725	0.989	0.000
DAY 29	MEAN	2722.4 d	2729.7	2677.9	2702.5	2171.0**
	S.D.	161.59	175.87	176.57	186.05	130.11
	N	21	20	21	17	2
	p-value	0.001	1.000	0.823	0.991	0.000

Statistical key: d=Dunnett's-test ** = p<0.01

MEAN BODY WEIGHTS CHANGES DURING GESTATION (GRAMS)

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAYS 0 TO 6	MEAN	5.9 d	15.8	14.4	-2.8	59.0
	S.D.	55.63	60.94	52.42	50.84	45.25
	N	21	20	21	17	2
	p-value	0.568				
DAYS 6 TO 7	MEAN	-8.5 d	-0.6	-8.6	-5.0	-13.0
	S.D.	26.12	27.25	29.09	23.46	42.43
	N	21	20	21	17	2
	p-value	0.852				
DAYS 7 TO 8	MEAN	-2.8 d	-3.1	-5.3	-2.2	-17.5
	S.D.	32.09	28.18	20.75	15.58	9.19
	N	21	20	21	17	2
	p-value	0.940				
DAYS 8 TO 9	MEAN	1.1 d	-3.8	3.2	-4.9	-2.0
	S.D.	27.84	25.52	22.03	28.58	1.41
	N	21	20	21	17	2
	p-value	0.859				
DAYS 9 TO 10	MEAN	5.1 d	-3.5	6.9	-1.1	-10.0
	S.D.	22.02	19.83	15.56	18.40	36.77
	N	21	20	21	17	2
	p-value	0.334				
DAYS 10 TO 11	MEAN	-3.7 d	13.3	-4.2	9.2	-17.5
	S.D.	26.34	20.21	19.74	24.06	26.16
	N	21	20	21	17	2
	p-value	0.036	0.065	1.000	0.257	0.879
DAYS 11 TO 12	MEAN	-0.1 d	-5.8	2.9	-9.2	-9.0
	S.D.	27.15	22.20	19.45	32.24	22.63
	N	21	20	21	17	2
	p-value	0.596				
DAYS 12 TO 13	MEAN	12.4 d	15.5	2.7	10.1	-33.5*
	S.D.	17.17	20.93	28.14	22.16	23.33
	N	21	20	21	17	2
	p-value	0.034	0.978	0.436	0.994	0.028
DAYS 13 TO 14	MEAN	13.9 d	7.2	10.3	13.2	10.0
	S.D.	26.97	22.19	20.48	21.38	4.24
	N	21	20	21	17	2
	p-value	0.897				
DAYS 14 TO 15	MEAN	19.0 d	22.5	22.8	14.7	-14.0
	S.D.	22.06	18.57	21.01	15.61	11.31
	N	21	20	21	17	2
	p-value	0.106				
DAYS 15 TO 16	MEAN	21.2 d	13.4	17.2	14.0	-4.0
	S.D.	21.66	21.74	21.28	24.81	14.14
	N	21	20	21	17	2
	p-value	0.518				

Statistical key: d=Dunnett's-test * = p<0.05

MEAN BODY WEIGHTS CHANGES DURING GESTATION (GRAMS)

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAYS 16 TO 17	MEAN	14.3 d	9.9	8.1	1.4	18.5
	S.D.	23.73	22.04	19.78	27.14	34.65
	N	21	20	21	17	2
	p-value	0.511				
DAYS 17 TO 18	MEAN	-2.0 d	1.1	-2.7	-4.9	-18.0
	S.D.	22.15	20.28	16.29	21.81	0.00
	N	21	20	21	17	2
	p-value	0.718				
DAYS 18 TO 19	MEAN	-4.0 d	3.8	4.4	17.6**	-4.5
	S.D.	20.09	14.75	15.41	27.55	24.75
	N	21	20	21	17	2
	p-value	0.025	0.537	0.453	0.005	1.000
DAYS 19 TO 20	MEAN	1.0 d	6.0	0.9	-7.9	-18.0
	S.D.	18.38	20.07	24.62	20.08	2.83
	N	21	20	21	17	2
	p-value	0.234				
DAYS 20 TO 21	MEAN	4.4 d	-0.2	3.8	10.3	-4.0
	S.D.	18.12	17.29	11.57	19.77	18.38
	N	21	20	21	17	2
	p-value	0.406				
DAYS 21 TO 22	MEAN	12.0 d	16.0	16.2	8.4	7.0
	S.D.	19.40	19.67	16.90	16.43	11.31
	N	21	20	21	17	2
	p-value	0.635				
DAYS 22 TO 23	MEAN	9.0 d	14.1	20.1	15.2	7.0
	S.D.	17.50	24.55	15.14	22.82	29.70
	N	21	20	21	17	2
	p-value	0.489				
DAYS 23 TO 24	MEAN	17.5 d	22.6	21.1	10.2	-5.0
	S.D.	20.59	27.21	15.95	11.07	14.14
	N	21	20	21	17	2
	p-value	0.152				
DAYS 24 TO 25	MEAN	32.2 d	26.6	25.8	25.2	18.5
	S.D.	16.86	17.24	18.44	20.29	10.61
	N	21	20	21	17	2
	p-value	0.660				
DAYS 25 TO 26	MEAN	13.0 d	17.9	26.2	16.1	9.5
	S.D.	17.48	14.96	18.04	14.54	3.54
	N	21	20	21	17	2
	p-value	0.101				
DAYS 26 TO 27	MEAN	24.3 d	21.5	22.8	19.1	-51.5**
	S.D.	17.84	23.63	14.22	20.14	54.45
	N	21	20	21	17	2
	p-value	0.000	0.977	0.997	0.851	0.000

Statistical key: d=Dunnett's-test ** = p<0.01

MEAN BODY WEIGHTS CHANGES DURING GESTATION (GRAMS)

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
DAYS 27 TO 28	MEAN	13.9 d	18.7	13.4	11.7	4.5
	S.D.	15.72	16.10	18.87	21.99	4.95
	N	21	20	21	17	2
	p-value	0.701				
DAYS 28 TO 29	MEAN	25.8 d	28.5	32.8	26.3	-8.0
	S.D.	20.83	23.17	20.16	21.38	16.97
	N	21	20	21	17	2
	p-value	0.144				
DAYS 0 TO 6	MEAN	5.9 d	15.8	14.4	-2.8	59.0
	S.D.	55.63	60.94	52.42	50.84	45.25
	N	21	20	21	17	2
	p-value	0.568				
DAYS 6 TO 29	MEAN	219.0 d	241.6	240.9	187.5	-154.5**
	S.D.	105.19	133.72	115.88	80.03	37.48
	N	21	20	21	17	2
	p-value	0.000	0.914	0.918	0.810	0.000
DAYS 0 TO 29	MEAN	224.9 d	257.4	255.2	184.7	-95.5**
	S.D.	140.48	161.24	137.74	98.15	82.73
	N	21	20	21	17	2
	p-value	0.009	0.865	0.884	0.794	0.009

Statistical key: d=Dunnett's-test ** = p<0.01

T0061724 MKH 6561

MEAN UTERINE WEIGHTS AND CORRECTED BODY WEIGHTS CHANGES (GRAMS)

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
GRAVID UTERUS	MEAN	364.0 d	383.0	369.5	321.6	183.5
	S.D.	87.80	119.26	101.34	92.07	41.72
	N	21	20	21	17	2
	p-value	0.052				
CARCASS	MEAN	2358.4 d	2346.6	2308.4	2380.9	1987.5**
	S.D.	148.79	146.08	149.82	175.63	171.83
	N	21	20	21	17	2
	p-value	0.018	0.998	0.679	0.979	0.007
CORRECTED WEIGHT CHANGE FROM DAY 0 TO 29	MEAN	-139.1 d	-125.7	-114.2	-136.9	-279.0
	S.D.	121.66	163.19	109.66	100.43	41.01
	N	21	20	21	17	2
	p-value	0.516				

Statistical key: d=Dunnett's-test ** = p<0.01

CARCASS WEIGHT = BODY WEIGHT DAY 29 MINUS UTERINE WEIGHT
CORRECTED WEIGHT CHANGE DAY 0 TO 29 = CARCASS WEIGHT MINUS DAY 0 BODY WEIGHT

Medical Laboratory Examination

007594/98.001

	ASAT (GOT) U/l	ALAT (GPT) U/l	APh U/l	GLDH U/l	GGT U/l	CHOL mmol/l	TRIGL mmol/l	BILI-t mcmol/l
0 mg/kg								
Mean	19.7	38.1	78	5.6	4	0.29	0.35	1.0
Med.	17.8	36.1	71	3.7	4	0.29	0.32	1.0
S.D.	9.01	10.46	23.0	3.92	0.9	0.063	0.189	0.21
Min.	10.8	25.2	57	2.1	3	0.20	0.18	0.7
Max.	37.3	54.3	132	15.2	6	0.40	0.85	1.4
N	10	10	10	10	10	10	10	10
MKH 6561 20 mg/kg								
Mean	19.2	40.4	72	5.5	5	0.29	0.29	0.9
Med.	17.8	37.5	62	5.7	5	0.25	0.28	0.9
S.D.	8.86	7.16	17.4	3.21	0.7	0.111	0.100	0.18
Min.	7.3	31.1	54	1.4	4	0.15	0.15	0.7
Max.	32.8	49.8	102	11.6	6	0.48	0.45	1.2
N	9	9	9	9	9	9	9	9
TS 1%	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-
MKH 6561 100 mg/kg								
Mean	18.7	39.3	66	5.2	5	0.29	0.33	0.9
Med.	19.9	39.0	61	5.1	5	0.30	0.26	0.9
S.D.	5.77	6.05	12.8	2.51	1.3	0.089	0.220	0.12
Min.	4.3	30.9	52	2.2	3	0.16	0.18	0.7
Max.	24.7	49.6	89	9.1	8	0.44	0.89	1.1
N	10	10	10	10	10	10	10	10
TS 1%	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-
MKH 6561 500 mg/kg								
Mean	16.4	38.7	63	6.6	4	0.29	0.29	1.0
Med.	12.6	36.4	67	4.3	4	0.31	0.24	1.0
S.D.	11.23	8.66	17.0	6.98	0.8	0.074	0.155	0.11
Min.	7.1	28.6	40	1.7	4	0.16	0.10	0.9
Max.	40.7	55.6	85	21.6	6	0.38	0.59	1.2
N	7	7	7	7	7	7	7	7
TS 1%	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-
MKH 6561 1000 mg/kg								
Mean	12.6	25.3	52	6.2	3	0.80	0.40	3.2
Med.	12.6	25.3	52	6.2	3	0.80	0.40	3.2
S.D.	9.12	5.73	8.5	7.21	1.4	0.120	0.049	0.35
Min.	6.1	21.2	46	1.1	2	0.71	0.36	2.9
Max.	19.0	29.3	58	11.3	4	0.88	0.43	3.4
N	2	2	2	2	2	2	2	2
TS 1%	nc	nc	nc	nc	nc	nc	nc	nc
TS 5%	nc	nc	nc	nc	nc	nc	nc	nc

Medical Laboratory Examination

007594/98.002

	PROT	ALBUMIN	T3	T4	TBC	PT
	g/l	g/l	nmol/l	nmol/l	TBI	sec
0 mg/kg						
Mean	51.6	33.6	1.67	35	0.76	6.5
Med.	51.1	33.6	1.61	35	0.75	6.5
S.D.	4.68	3.52	0.254	8.3	0.078	0.38
Min.	44.2	29.3	1.38	23	0.63	6.0
Max.	59.4	39.9	2.11	49	0.85	7.3
N	10	10	10	10	10	10
MKH 6561 20 mg/kg						
Mean	54.3	34.5	1.76	37	0.75	6.7
Med.	52.5	34.8	1.81	38	0.75	6.5
S.D.	7.97	4.13	0.185	6.3	0.078	0.75
Min.	41.5	26.9	1.46	27	0.66	6.1
Max.	67.0	41.3	2.08	44	0.92	8.6
N	9	9	9	9	9	9
TS 1%	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-
MKH 6561 100 mg/kg						
Mean	50.7	33.3	1.76	39	0.79	6.4
Med.	49.4	32.2	1.75	41	0.81	6.5
S.D.	6.15	4.35	0.198	7.4	0.064	0.20
Min.	43.5	27.4	1.50	25	0.69	6.1
Max.	62.7	40.3	2.11	52	0.90	6.7
N	10	10	10	10	10	10
TS 1%	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-
MKH 6561 500 mg/kg						
Mean	53.8	33.6	1.59	37	0.72	6.4
Med.	52.8	33.2	1.63	36	0.73	6.4
S.D.	4.99	2.90	0.139	8.2	0.084	0.16
Min.	48.2	29.9	1.30	25	0.59	6.1
Max.	61.7	37.6	1.74	48	0.82	6.6
N	7	7	7	7	7	7
TS 1%	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-
MKH 6561 1000 mg/kg						
Mean	47.8	31.3	0.38	15	0.86	6.3
Med.	47.8	31.3	0.38	15	0.86	6.3
S.D.	2.05	1.06	0.064	0.7	0.028	0.21
Min.	46.4	30.5	0.33	14	0.84	6.1
Max.	49.3	32.0	0.42	15	0.88	6.4
N	2	2	2	2	2	2
TS 1%	nc	nc	nc	nc	nc	nc
TS 5%	nc	nc	nc	nc	nc	nc

Medical Laboratory Examination

Mean values of females with abortion in the 1000 mg/kg group

Dose (mg/kg b.w./day)		1000
ASAT	(U/l)	14.7
ALAT	(U/l)	49.8
APh	(U/l)	52.2
GLDH	(U/l)	12.7
GGT	(U/l)	3.5
CHOL	(mmol/l)	1.7
TRIGL	(mmol/l)	0.8
BILI-t	(mcmol/l)	2.5
PROT	(g/l)	50.9
ALBUMIN	(g/l)	33.5
T3	(nmol/l)	0.54
T4	(nmol/l)	24.9
TBC	(TBI)	0.84
PT	(sec)	6.8

T0061724 MKH 6561

SUMMARY OF NECROPSY OBSERVATIONS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
FEMALES	N	22	22	22	22	22
STOMACH	N	0	0	0	0	2
CONTENTS SOLID	N	0	0	0	0	2
SMALL INTESTINE	N	0	0	0	0	3
LIGHT DISCOLORED	N	0	0	0	0	3
CAECUM	N	0	0	0	11	22
ENLARGED	N	0	0	0	11	22
CONTENTS GASEOUS	N	0	0	0	0	21
CONTENTS FLUID	N	0	0	0	0	20
LIVER	N	2	0	1	1	3
DISCOLORATION	N	0	0	0	1	0
DISTINCT LOBULATION	N	0	0	0	1	2
VESICLE	N	1	0	0	0	1
ADDITIONAL TISSUE	N	0	0	1	0	0
GREY-WHITISH PUNCTIFORM AREA(S)	N	1	0	0	0	1
LOBE BIPARTITE	N	0	0	0	0	1
GALL BLADDER	N	0	0	0	0	1
MISSING	N	0	0	0	0	1
RECTUM	N	2	0	0	3	2
CONTENTS GASEOUS	N	2	0	0	3	2

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MKH 6561

SUMMARY OF NECROPSY OBSERVATIONS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
FEMALES	N	22	22	22	22	22
URINARY BLADDER						
TIGHTLY FILLED	N	1	1	0	2	1
OVIDUCT	N	4	6	6	3	1
CYST(S)	N	4	6	6	3	1
NO REMARKABLE OBSERVATIONS	N	15	16	15	10	0

T0061724

MKH 6561

MEAN ORGAN WEIGHTS
ABSOLUTE ORGAN WEIGHTS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
FINAL BODY WEIGHT g	Mean	2656.1 d	2600.3	2601.0	2664.0	2171.0**
	S.D.	113.11	83.87	103.10	204.40	130.11
	N	10	9	10	7	2
	p-value	0.001	0.752	0.735	1.000	0.000
LIVER g	Mean	57.416 d	55.560	58.480	58.993	43.865
	S.D.	8.6970	3.9446	9.1817	6.4195	6.8943
	N	10	9	10	7	2
	p-value	0.145				

Statistical key: d=Dunnett's-test ** = p<0.01

T0061724 MKH 6561

MEAN ORGAN WEIGHTS
ORGAN WEIGHT TO BODY WEIGHT RATIO

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
FINAL BODY WEIGHT g	Mean	2656.1 d	2600.3	2601.0	2664.0	2171.0**
	S.D.	113.11	83.87	103.10	204.40	130.11
	N	10	9	10	7	2
	p-value	0.001	0.752	0.735	1.000	0.000
LIVER Ratio	Mean	0.0216 d	0.0214	0.0225	0.0222	0.0201
	S.D.	.00286	.00161	.00365	.00294	.00197
	N	10	9	10	7	2
	p-value	0.789				

Statistical key: d=Dunnett's-test ** = p<0.01

T0061724

MKH 6561

MEAN ORGAN WEIGHTS
ABSOLUTE ORGAN WEIGHTS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
CARCASS WEIGHT g	Mean	2299.6 d	2269.0	2245.5	2339.3	1987.5*
	S.D.	103.81	141.83	124.50	155.44	171.83
	N	10	9	10	7	2
	p-value	0.032	0.964	0.767	0.938	0.017
LIVER g	Mean	57.416 d	55.560	58.480	58.993	43.865
	S.D.	8.6970	3.9446	9.1817	6.4195	6.8943
	N	10	9	10	7	2
	p-value	0.145				

Statistical key: d=Dunnett's-test * = p<0.05
CARCASS WEIGHT = BODY WEIGHT AT TERMINATION MINUS UTERINE WEIGHT

T0061724

MKH 6561

MEAN ORGAN WEIGHTS
ORGAN WEIGHT TO CARCASS WEIGHT RATIO

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
CARCASS WEIGHT g	Mean	2299.6 d	2269.0	2245.5	2339.3	1987.5*
	S.D.	103.81	141.83	124.50	155.44	171.83
	N	10	9	10	7	2
	p-value	0.032	0.964	0.767	0.938	0.017
LIVER Ratio	Mean	0.0249 d	0.0245	0.0260	0.0253	0.0220
	S.D.	.00312	.00126	.00341	.00288	.00157
	N	10	9	10	7	2
	p-value	0.425				

Statistical key: d=Dunnett's-test * = p<0.05
CARCASS WEIGHT = BODY WEIGHT AT TERMINATION MINUS UTERINE WEIGHT

T0061724

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SUMMARY OF CESAREAN SECTION DATA

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Number of females						
with implantations (a)		21	20	21	18	2
with viable fetuses (b)		21	20	21	17	2
Corpora Lutea						
per group		172	161	184	138	20
per female: mean		8.2 d	8.1	8.8	7.7	10.0
st. dev.		1.78	2.46	1.61	1.78	2.83
n (a)		21	20	21	18	2
	p-value	0.307				
Corpora Lutea						
per group		172	161	184	135	20
per female: mean		8.2 d	8.1	8.8	7.9	10.0
st. dev.		1.78	2.46	1.61	1.39	2.83
n (b)		21	20	21	17	2
	p-value	0.421				
Implantations						
per group		156 f	151	162	124	14
% of Corpora lutea		90.7	93.8	88.0	89.9	70.0
	p-value	0.016	1.000	1.000	1.000	0.060
per female: mean		7.4 d	7.6	7.7	6.9	7.0
st. dev.		1.91	2.54	2.37	2.11	1.41
n (a)		21	20	21	18	2
	p-value	0.824				
Implantations						
per group		156 f	151	162	121	14
% of Corpora lutea		90.7	93.8	88.0	89.6	70.0
	p-value	0.016	1.000	1.000	1.000	0.060
per female: mean		7.4 d	7.6	7.7	7.1	7.0
st. dev.		1.91	2.54	2.37	1.93	1.41
n (b)		21	20	21	17	2
	p-value	0.936				

Statistical key: d=Dunnett's-test f=Fisher's Exact

SUMMARY OF CESAREAN SECTION DATA

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Number of females						
with implantations (a)		21	20	21	18	2
with viable fetuses (b)		21	20	21	17	2
Postimplantation Loss						
total per group		10 f	6	12	14	4
% of implantations		6.4	4.0	7.4	11.3	28.6
	p-value	0.006	1.000	1.000	0.787	0.072
per female: mean		0.5 k	0.3	0.6	0.8	2.0
st. dev.		0.98	0.57	0.60	1.06	0.00
n (a)		21	20	21	18	2
	p-value	0.051				
No. of females affected		6	5	11	8	2
Postimplantation Loss						
total per group		10 f	6	12	11	4
% of implantations		6.4	4.0	7.4	9.1	28.6
	p-value	0.012	1.000	1.000	1.000	0.072
per female: mean		0.5 k	0.3	0.6	0.6	2.0
st. dev.		0.98	0.57	0.60	0.93	0.00
n (b)		21	20	21	17	2
	p-value	0.055				
No. of females affected		6	5	11	7	2
Dead Fetuses						
per group		0 f	0	0	0	0
% of implantations		0.0	0.0	0.0	0.0	0.0
	p-value	1.000				
per female: mean		0.0 k	0.0	0.0	0.0	0.0
st. dev.		0.00	0.00	0.00	0.00	0.00
n (a)		21	20	21	18	2
	p-value	1.000				
No. of females affected		0	0	0	0	0
Dead Fetuses						
per group		0 f	0	0	0	0
% of implantations		0.0	0.0	0.0	0.0	0.0
	p-value	1.000				
per female: mean		0.0 k	0.0	0.0	0.0	0.0
st. dev.		0.00	0.00	0.00	0.00	0.00
n (b)		21	20	21	17	2
	p-value	1.000				
No. of females affected		0	0	0	0	0

Statistical key: f=Fisher's Exact k=Kruskal-Wallis

SUMMARY OF CESAREAN SECTION DATA

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Number of females						
with implantations (a)		21	20	21	18	2
with viable fetuses (b)		21	20	21	17	2
Early Resorptions						
per group		0 f	0	0	3	0
% of implantations		0.0	0.0	0.0	2.4	0.0
	p-value	0.019			0.343	
per female: mean		0.0 k	0.0	0.0	0.2	0.0
st. dev.		0.00	0.00	0.00	0.71	0.00
n (a)		21	20	21	18	2
	p-value	0.469				
No. of females affected		0	0	0	1	0
Early Resorptions						
per group		0 f	0	0	0	0
% of implantations		0.0	0.0	0.0	0.0	0.0
	p-value	1.000				
per female: mean		0.0 k	0.0	0.0	0.0	0.0
st. dev.		0.00	0.00	0.00	0.00	0.00
n (b)		21	20	21	17	2
	p-value	1.000				
No. of females affected		0	0	0	0	0
Late Resorptions						
per group		10 f	6	12	11	4
% of implantations		6.4	4.0	7.4	8.9	28.6
	p-value	0.012	1.000	1.000	1.000	0.072
per female: mean		0.5 k	0.3	0.6	0.6	2.0
st. dev.		0.98	0.57	0.60	0.92	0.00
n (a)		21	20	21	18	2
	p-value	0.058				
No. of females affected		6	5	11	7	2
Late Resorptions						
per group		10 f	6	12	11	4
% of implantations		6.4	4.0	7.4	9.1	28.6
	p-value	0.012	1.000	1.000	1.000	0.072
per female: mean		0.5 k	0.3	0.6	0.6	2.0
st. dev.		0.98	0.57	0.60	0.93	0.00
n (b)		21	20	21	17	2
	p-value	0.055				
No. of females affected		6	5	11	7	2

Statistical key: f=Fisher's Exact k=Kruskal-Wallis

SUMMARY OF CESAREAN SECTION DATA

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Number of females						
with implantations (a)		21	20	21	18	2
with viable fetuses (b)		21	20	21	17	2
Live Fetuses						
per group		146	145	150	110	10
per female: mean		7.0 d	7.3	7.1	6.5	5.0
st. dev.		2.11	2.67	2.35	2.24	1.41
n (b)		21	20	21	17	2
	p-value	0.636				
% of Implantations						
per group		93.6 f	96.0	92.6	90.9	71.4
	p-value	0.012	1.000	1.000	1.000	0.072
per female: mean		93.1 d	95.1	92.4	90.1	70.8
st. dev.		13.48	11.67	8.28	15.58	5.89
n (b)		21	20	21	17	2
	p-value	0.112				
Sex Ratio of Fetuses						
per group						
males		76 f	74	73	62	5
% males		52.1	51.0	48.7	56.4	50.0
	p-value	0.817				
females		70 f	71	77	48	5
% females		47.9	49.0	51.3	43.6	50.0
	p-value	0.817				
not determinable		0 f	0	0	0	0
% not determinable		0.0	0.0	0.0	0.0	0.0
	p-value	1.000				
Litter Mean						
% males: mean		50.0 k	50.8	49.9	55.5	50.0
st. dev.		20.66	19.20	22.57	21.04	0.00
n (b)		21	20	21	17	2
	p-value	0.877				
% females: mean		50.0 k	49.2	50.1	44.5	50.0
st. dev.		20.66	19.20	22.57	21.04	0.00
n (b)		21	20	21	17	2
	p-value	0.877				
% not determinable: mean		0.0 k	0.0	0.0	0.0	0.0
st. dev.		0.00	0.00	0.00	0.00	0.00
n (b)		21	20	21	17	2
	p-value	1.000				

Statistical key: d=Dunnett's-test f=Fisher's Exact k=Kruskal-Wallis

SUMMARY OF CESAREAN SECTION DATA

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Number of females						
with implantations (a)		21	20	21	18	2
with viable fetuses (b)		21	20	21	17	2
Preimplantation Loss						
per group		16 f	10	22	14	6
% of Corpora lutea		9.3	6.2	12.0	10.1	30.0
	p-value	0.016	1.000	1.000	1.000	0.060
per female: mean		0.8 k	0.5	1.0	0.8	3.0
st. dev.		1.34	0.83	2.13	1.35	4.24
n (a)		21	20	21	18	2
	p-value	0.925				
No. of females affected		7	7	7	7	1
Preimplantation Loss						
per group		16 f	10	22	14	6
% of Corpora lutea		9.3	6.2	12.0	10.4	30.0
	p-value	0.016	1.000	1.000	1.000	0.060
per female: mean		0.8 k	0.5	1.0	0.8	3.0
st. dev.		1.34	0.83	2.13	1.38	4.24
n (b)		21	20	21	17	2
	p-value	0.912				
No. of females affected		7	7	7	7	1
Placental Weight						
Litter Basis						
n (litters)		21	20	21	17	2
mean (g)		4.33 d	4.46	4.25	3.94	3.15
st. dev.		0.684	0.768	0.624	0.555	0.061
	p-value	0.030	0.920	0.988	0.238	0.074

Statistical key: d=Dunnett's-test f=Fisher's Exact k=Kruskal-Wallis

SUMMARY OF CESAREAN SECTION DATA

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Number of females						
with implantations (a)		21	20	21	18	2
with viable fetuses (b)		21	20	21	17	2
Weight of Live Fetuses						
Litter Basis						
total fetuses						
mean (g)		37.29 d	37.48	36.87	35.25	23.14**
st. dev.		3.421	3.180	4.418	3.172	2.168
n (litters)		21	20	21	17	2
	p-value	0.000	0.999	0.987	0.258	0.000
male fetuses						
mean (g)		37.72 d	37.59	37.13	35.40	23.09**
st. dev.		3.700	3.701	4.846	3.407	1.784
n (litters)		20	20	21	17	2
	p-value	0.000	1.000	0.970	0.243	0.000
female fetuses						
mean (g)		36.58 d	37.48	36.21	35.76	23.19**
st. dev.		3.366	2.810	4.404	4.367	2.551
n (litters)		21	20	20	17	2
	p-value	0.000	0.860	0.993	0.913	0.000

Statistical key: d=Dunnett's-test ** = p<0.01

SUMMARY OF PLACENTAL OBSERVATIONS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Litters Evaluated	N	21	20	21	17	2
Fetuses Evaluated	N	146	145	150	110	10
Live	N	146	145	150	110	10
Dead	N	0	0	0	0	0
PLACENTA						
PLACENTA PARTLY NECROTIC						
Fetal Incidence	N	3	1	1	0	0
	%	2.1	0.7	0.7	0.0	0.0
Litter Incidence	N	3	1	1	0	0
	%	14.3	5.0	4.8	0.0	0.0
Affected Fetuses/Litter	MEAN%	1.96	0.71	0.79	0.00	0.00
	S.D.	4.920	3.194	3.637	0.000	0.000
PLACENTA COARSE-GRAINED						
Fetal Incidence	N	0	0	0	3	10
	%	0.0	0.0	0.0	2.7	100.0
Litter Incidence	N	0	0	0	1	2
	%	0.0	0.0	0.0	5.9	100.0
Affected Fetuses/Litter	MEAN%	0.00	0.00	0.00	5.88	100.00
	S.D.	0.000	0.000	0.000	24.254	0.000
PALE						
Fetal Incidence	N	0	0	0	0	4
	%	0.0	0.0	0.0	0.0	40.0
Litter Incidence	N	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	50.0
Affected Fetuses/Litter	MEAN%	0.00	0.00	0.00	0.00	50.00
	S.D.	0.000	0.000	0.000	0.000	70.711
TOTAL PLACENTAL OBSERVATIONS						
Fetal Incidence	N	3	1	1	3	10
	%	2.1	0.7	0.7	2.7	100.0
Litter Incidence	N	3	1	1	1	2
	%	14.3	5.0	4.8	5.9	100.0

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SUMMARY OF FETAL EXTERNAL OBSERVATIONS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Litters Evaluated	N	21	20	21	17	2
Fetuses Evaluated	N	146	145	150	110	10
Live	N	146	145	150	110	10
Dead	N	0	0	0	0	0
PALATE						
CYST						
Fetal Incidence	N	0	1	0	0	0
	%	0.0	0.7	0.0	0.0	0.0
Litter Incidence	N	0	1	0	0	0
	%	0.0	5.0	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.00	0.63	0.00	0.00	0.00
	S.D.	0.000	2.795	0.000	0.000	0.000
LIMBS						
MALPOSITION OF FORELIMB(S)						
Fetal Incidence	N	3	2	5	0	0
	%	2.1	1.4	3.3	0.0	0.0
Litter Incidence	N	3	1	4	0	0
	%	14.3	5.0	19.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	2.07	1.43	2.88	0.00	0.00
	S.D.	5.235	6.389	7.039	0.000	0.000

SUMMARY OF FETAL VISCERAL OBSERVATIONS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Litters Evaluated	N	21	20	21	17	2
Fetuses Evaluated	N	146	145	150	110	10
Live	N	146	145	150	110	10
Dead	N	0	0	0	0	0
PALATE						
CYST						
Fetal Incidence	N	0	1	0	0	0
	%	0.0	0.7	0.0	0.0	0.0
Litter Incidence	N	0	1	0	0	0
	%	0.0	5.0	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.00	0.63	0.00	0.00	0.00
	S.D.	0.000	2.795	0.000	0.000	0.000
HEART						
VENTRICULAR SEPTAL DEFECT						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.7	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.8	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.00	0.00	0.68	0.00	0.00
	S.D.	0.000	0.000	3.117	0.000	0.000
ABDOMINAL CAVITY						
REDDISH FLUID IN ABDOMINAL CAVITY						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.7	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.8	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.00	0.00	0.40	0.00	0.00
	S.D.	0.000	0.000	1.818	0.000	0.000

SUMMARY OF FETAL VISCERAL OBSERVATIONS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Litters Evaluated	N	21	20	21	17	2
Fetuses Evaluated	N	146	145	150	110	10
Live	N	146	145	150	110	10
Dead	N	0	0	0	0	0
LIVER						
DISTINCT LIVER LOBULATION						
Fetal Incidence	N	17	22	5	12	4
	%	11.6	15.2	3.3	10.9	40.0
Litter Incidence	N	4	5	2	2	1
	%	19.0	25.0	9.5	11.8	50.0
Affected Fetuses/Litter	MEAN%	9.06	13.39	2.18	9.15	50.00
	S.D.	24.101	31.285	7.640	26.999	70.711
SMALL ACCESSORY LIVER LOBE						
Fetal Incidence	N	0	0	0	1	0
	%	0.0	0.0	0.0	0.9	0.0
Litter Incidence	N	0	0	0	1	0
	%	0.0	0.0	0.0	5.9	0.0
Affected Fetuses/Litter	MEAN%	0.00	0.00	0.00	0.59	0.00
	S.D.	0.000	0.000	0.000	2.425	0.000
SEVERAL GLASSY VESICLES ON THE RIGHT LOWER LIVER LOBE						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.7	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.8	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.00	0.00	0.68	0.00	0.00
	S.D.	0.000	0.000	3.117	0.000	0.000

SUMMARY OF FETAL VISCERAL OBSERVATIONS

		0 MG/KG	20 MG/KG	100 MG/KG	500 MG/KG	1000 MG/KG
Litters Evaluated	N	21	20	21	17	2
Fetuses Evaluated	N	146	145	150	110	10
Live	N	146	145	150	110	10
Dead	N	0	0	0	0	0
KIDNEY						
DILATION OF RENAL PELVIS						
Fetal Incidence	N	0	1	0	0	0
	%	0.0	0.7	0.0	0.0	0.0
Litter Incidence	N	0	1	0	0	0
	%	0.0	5.0	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.00	0.71	0.00	0.00	0.00
	S.D.	0.000	3.194	0.000	0.000	0.000

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Fetal Head Observations (Mod. Wilson Technique)

Incidence Table

Fingings	Dose in mg/kg 0	20	100	500	1000
palate - cyst at the rear part filled with fluid	0	1	0	0	0

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SUMMARY OF FETAL SKELETAL OBSERVATIONS

		0 MG/KG		20 MG/KG		100 MG/KG		500 MG/KG		1000 MG/KG	
Number of fetuses		146		145		150		110		10	
		Number	%	Number	%	Number	%	Number	%	Number	%
MEDIAL PHALANX DIGIT(S)											
-INCOMPLETELY OSSIFIED											
5th	right	17	11.6	16	11.0	25	16.7	26	23.6	8**	80.0
-UNOSSIFIED											
5th	right	0	0.0	0	0.0	0	0.0	1	0.9	2*	20.0
-INCOMPLETELY OSSIFIED											
4th	left	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
5th	left	17	11.6	16	11.0	25	16.7	25	22.7	8**	80.0
-UNOSSIFIED											
5th	left	0	0.0	0	0.0	1	0.7	2	1.8	2*	20.0
PROXIMAL PHALANX DIGIT(S)											
-INCOMPLETELY OSSIFIED											
1st	right	0	0.0	0	0.0	0	0.0	0	0.0	1	10.0
-INCOMPLETELY OSSIFIED											
1st	left	0	0.0	0	0.0	0	0.0	0	0.0	1	10.0
METACARPALS											
-INCOMPLETELY OSSIFIED											
1st	right	4	2.7	0	0.0	6	4.0	9	8.2	6**	60.0
-UNOSSIFIED											
1st	right	0	0.0	0	0.0	0	0.0	0	0.0	2*	20.0
-INCOMPLETELY OSSIFIED											
1st	left	4	2.7	0	0.0	6	4.0	9	8.2	7**	70.0
-UNOSSIFIED											
1st	left	0	0.0	0	0.0	0	0.0	0	0.0	1	10.0

Statistical key: f=Fisher's Exact * = $p<0.05$ ** = $p<0.01$

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SUMMARY OF FETAL SKELETAL OBSERVATIONS

	0 MG/KG		20 MG/KG		100 MG/KG		500 MG/KG		1000 MG/KG	
Number of fetuses	146		145		150		110		10	
	Number	%	Number	%	Number	%	Number	%	Number	%
MEDIAL PHALANX TOE(S)										
-INCOMPLETELY OSSIFIED 5th right	11	7.5	13	9.0	22	14.7	17	15.5	10**	100.0
-INCOMPLETELY OSSIFIED 5th left	12	8.2	11	7.6	21	14.0	15	13.6	10**	100.0
TALUS										
-INCOMPLETELY OSSIFIED bilateral	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0

Statistical key: f=Fisher's Exact ** = p<0.01

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SUMMARY OF FETAL SKELETAL OBSERVATIONS

	0 MG/KG		20 MG/KG		100 MG/KG		500 MG/KG		1000 MG/KG	
Number of fetuses	146		145		150		110		10	
	Number	%	Number	%	Number	%	Number	%	Number	%
STERNEBRA(E)										
-INCOMPLETELY OSSIFIED										
1st	0	0.0	1	0.7	1	0.7	2	1.8	0	0.0
2nd	1	0.7	2	1.4	2	1.3	1	0.9	0	0.0
3rd	1	0.7	1	0.7	0	0.0	0	0.0	0	0.0
4th	1	0.7	5	3.4	1	0.7	2	1.8	0	0.0
5th	111	76.0	96	66.2	114	76.0	85	77.3	9	90.0
6th	12	8.2	9	6.2	7	4.7	5	4.5	0	0.0
-UNOSSIFIED										
5th	32	21.9	41	28.3	34	22.7	17	15.5	0	0.0
-ASYMMETRICAL										
2nd	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0
3rd	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0
4th	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0
-SUPERNUMERARY OSSIFICATION CENTER										
	1	0.7	0	0.0	1	0.7	0	0.0	0	0.0
-BIFURCATION										
6th	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
-FUSION										
	3	2.1	3	2.1	9	6.0	4	3.6	0	0.0

Statistical key: f=Fisher's Exact

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SUMMARY OF FETAL SKELETAL OBSERVATIONS

		0 MG/KG		20 MG/KG		100 MG/KG		500 MG/KG		1000 MG/KG	
Number of fetuses		146		145		150		110		10	
		Number	%	Number	%	Number	%	Number	%	Number	%
RIB(S)											
-SHORTENED (SLIGHTLY)											
3rd	right	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
12th	right	1	0.7	1	0.7	0	0.0	0	0.0	0	0.0
-SHORTENED (SLIGHTLY)											
12th	left	1	0.7	0	0.0	0	0.0	1	0.9	0	0.0
-FUSION											
	left	1	0.7	0	0.0	1	0.7	0	0.0	0	0.0
-THICKENED (SLIGHTLY)											
3rd	right	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
6th	right	1	0.7	1	0.7	0	0.0	1	0.9	0	0.0
7th	right	0	0.0	2	1.4	1	0.7	1	0.9	0	0.0
-THICKENED (SLIGHTLY)											
5th	left	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
6th	left	4	2.7	1	0.7	0	0.0	0	0.0	0	0.0
7th	left	6	4.1	3	2.1	2	1.3	4	3.6	0	0.0
8th	left	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0

Statistical key: f=Fisher's Exact

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SUMMARY OF FETAL SKELETAL OBSERVATIONS

		0 MG/KG		20 MG/KG		100 MG/KG		500 MG/KG		1000 MG/KG	
Number of fetuses		146		145		150		110		10	
		Number	%	Number	%	Number	%	Number	%	Number	%
12TH RIB											
-COMMA SHAPED											
	left	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
13TH RIB											
-PUNCTIFORM											
	left	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
-COMMA SHAPED											
	right	2	1.4	2	1.4	0	0.0	1	0.9	0	0.0
	bilateral	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0
-PRESENT (COMPLETELY OSSIFIED)											
	right	0	0.0	0	0.0	0	0.0	0	0.0	1	10.0
	left	1	0.7	1	0.7	0	0.0	0	0.0	0	0.0
-COMMA SHAPED AND FLOATING											
	left	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
-13th RIB SUM		2	1.4	5	3.4	0	0.0	2	1.8	1	10.0

Statistical key: f=Fisher's Exact

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SUMMARY OF FETAL SKELETAL OBSERVATIONS

	0 MG/KG		20 MG/KG		100 MG/KG		500 MG/KG		1000 MG/KG	
Number of fetuses	146		145		150		110		10	
	Number	%	Number	%	Number	%	Number	%	Number	%
CERVICAL VERTEBRAL BODY(IES)										
-INCOMPLETELY OSSIFIED										
1st	31	21.2	24	16.6	14*	9.3	15	13.6	0	0.0
6th	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0
-FLAT AND DUMBBELL SHAPED										
3rd right	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
-BIPARTITE										
3rd	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
4th	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
THORACIC VERTEBRAL BODY(IES)										
-DUMBBELL SHAPED										
2nd	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
6th	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
7th	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
-BIPARTITE										
3rd	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0

Statistical key: f=Fisher's Exact * = p<0.05

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SUMMARY OF FETAL SKELETAL OBSERVATIONS

	0 MG/KG		20 MG/KG		100 MG/KG		500 MG/KG		1000 MG/KG	
Number of fetuses	146		145		150		110		10	
	Number	%	Number	%	Number	%	Number	%	Number	%
LUMBAR VERTEBRA(E)										
-ONE MISSING	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
LUMBAR VERTEBRAL ARCH(ES)										
-INCOMPLETELY OSSIFIED 7th right	0	0.0	0	0.0	1	0.7	0	0.0	0	0.0
-INCOMPLETELY OSSIFIED 7th left	0	0.0	0	0.0	2	1.3	0	0.0	0	0.0
SACRAL VERTEBRAL ARCH(ES)										
-INCOMPLETELY OSSIFIED 2nd right	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
-INCOMPLETELY OSSIFIED 2nd left	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0

Statistical key: f=Fisher's Exact

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MKH 6561

SUMMARY OF FETAL SKELETAL OBSERVATIONS

		0 MG/KG		20 MG/KG		100 MG/KG		500 MG/KG		1000 MG/KG	
Number of fetuses		146		145		150		110		10	
		Number	%	Number	%	Number	%	Number	%	Number	%
CAUDAL VERTEBRAL ARCH(ES)											
-PRESENT											
1st	right	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
2nd	right	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
3rd	right	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
4th	right	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
5th	right	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
6th	right	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
7th	right	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
8th	right	40	27.4	30	20.7	41	27.3	57**	51.8	1	10.0
-PRESENT											
1st	left	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
2nd	left	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
3rd	left	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
4th	left	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
5th	left	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
6th	left	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
7th	left	146	100.0	145	100.0	150	100.0	110	100.0	10	100.0
8th	left	40	27.4	30	20.7	41	27.3	57**	51.8	1	10.0

Statistical key: f=Fisher's Exact ** = p<0.01